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Award Number: DAMD17-97-1-7353

TITLE: Epidemiological and Clinical Evidence for Residual Organophosphate Neurotoxicity

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REPORT DATE: October 2001

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

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20030214 177

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 2001	Final (25 Sep 97 - 24 Sep 01)

4. TITLE AND SUBTITLE
Epidemiological and Clinical Evidence for Residual Organophosphate Neurotoxicity

5. FUNDING NUMBERS
DAMD17-97-1-7353

6. AUTHOR(S)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***

We sought evidence to support or refute the proposal that Gulf War (GW) veterans who served in the Kuwaiti Theater of Operations (KTO) have nervous-system deficits consistent with prior exposure to organophosphorus chemicals (sarin and insecticides). Focus was placed on Desert Storm veterans present within a 50-km radius of Khamisiyah, Coalition-Occupied Iraq, who may have been exposed to sarin/cyclosarin during the first two weeks of March 1991 (Study Group). Comparison groups included other Desert Storm veterans with no known potential exposure to nerve agents and non-deployed GW-era veterans (negative controls). Veterans were given a computer-assisted telephone interview (CATI) to assess symptoms and exposures. Subjects completing the telephone interview were recruited for neurobehavioral testing and focused clinical neuromuscular and neurophysiological examination designed to detect any hallmarks of organophosphate-associated persistent central nervous system damage. Veterans who participated in or who witnessed the demolition at Khamisiyah in 1991 were more likely to report historical or extant symptoms when compared to veterans from other military units. However, no evidence was found of extant damage or dysfunction of neural pathways with reported or known susceptibility to sarin or other organophosphates.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Organophosphate, sarin, pyridostigmine, insecticide, behavior, neurophysiology, Khamisiyah	76
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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INTRODUCTION

We sought evidence to support or refute the proposal that Gulf War (GW) veterans who served in the Kuwaiti Theater of Operations (KTO) have nervous-system deficits consistent with prior exposure to organophosphorus chemicals (sarin and insecticides). Focus was placed on Desert Storm veterans present within a 50-km radius of Khamisiyah, Coalition-Occupied Iraq, who may have been exposed to sarin/cyclosarin during the first two weeks of March 1991 (Study Group). Comparison groups included other Desert Storm veterans with no known potential exposure to nerve agents and non-deployed GW-era veterans (negative controls). Veterans were given a computer-assisted telephone interview (CATI) to assess symptoms and exposures. Subjects completing the telephone interview were recruited for neurobehavioral testing (Level I). Level I employed a computerized neurobehavioral test battery. Level II testing comprised a focused clinical neuromuscular and neurophysiological examination designed to detect any hallmarks of organophosphate-associated persistent central nervous system (CNS) damage. The utilization of a cross-sectional survey of GW veterans with different exposure profiles, followed by a 2-level clinical examination, was designed to allow us to determine whether GW veterans who served in the KTO have nervous-system changes consistent with prior exposure to organophosphate chemicals.

BODY OF REPORT

Subject Recruitment and Location

The sampling pool for telephone interview consisted of 3219 veterans (923 in the Khamisiyah group, 927 non-Khamisiyah, and 1369 nondeployed) with telephone numbers tracked and located using Telematch, Equifax, IRS, Transunion and/or internet search engines. We were unable to enter a number of veterans into our sampling pool because of unavailable or untraceable telephone numbers. We compared veterans with locatable telephone numbers to those who could not be easily located. Veterans with locatable telephone numbers were more likely to have college or advanced degrees (24.0% compared to 15.4%, $p < 0.001$), to be married (57.2% compared to 47.2%, $p < 0.001$), to be Caucasian (68.8% compared to 60.1%, $p < 0.001$) and to be male (93.5% compared to 91.4%, $p = 0.002$).

We contacted by telephone 2918 of these 3219 veterans (90.6%). Of these 2918 individuals, 530 were contacted but found to be ineligible because they were not enrolled in the Army or National Guard during the GW (n = 274), they were veterans of prior conflicts and not the GW (n = 231), they had language or hearing problems that prevented administration of a telephone interview (n = 24), or were deceased (n=1). Of the 2918 individuals reached by telephone, 555 refused to complete the interview (19.0%), resulting in 1833 completed telephone interviews. Participants in the telephone survey, when compared to non-responders or persons who refused to participate, were more likely to be Caucasian (69.7% compared to 59.8%, $p < 0.001$) and to be on active versus reserve duty (83.1% compared to 73.4%, $p< 0.001$). There were no differences in the background characteristics of the initial 1524 responders compared to the 309

responders who were located with more intensive tracking mechanisms.

Level I: Neurobehavioral Testing

Level I neurobehavioral assessments were completed on 624 participants, in Portland, OR (87), Seattle, WA (65), Sacramento, CA (43), San Francisco, CA (44), Fayetteville, NC (231), and Hinesville, GA (154). These participants were present in Khamisiyah at the selected time (267), deployed in the KTO but not at Khamisiyah during the critical period (203 deployed), or not deployed in the KTO (154).

Huge disparities among volunteer mix emerged from the recruitment. The proportions of these groups differed in the various cities where testing was carried out. There was also a difference in the proportion of ethnicity among the participants who were in the various cities. The racial/ethnic groups included Caucasians (402), Hispanic-American (38), African American (130), Native American (4), Asian-American (13), Other (2), unspecified (35).

Data from neurobehavioral tests were extracted and comparisons made among the three veteran groups. Comparisons among these groups (Khamisiyah, non-Khamisiyah, and nondeployed) revealed significant group differences on some neurobehavioral tests (Simple Reaction Time, Oregon Dual Task, Tapping) and all psychological tests (Penn PTSD, Mississippi PTSD, multiple scales of the SF36, Beck Depression Scale). However, statistically significant differences also emerged among veterans in different cities and among the various ethnic groups. Differences among the deployment groups were clouded by differences among nominally comparable subjects residing in different cities and belonging to different ethnic groups. Extensive statistical analyses were employed to extract information independent of the regional differences, but clear answers did not emerge.

Level II: Neurophysiological Testing

A total of 98 individuals completed Level II testing (Table 1). Of these individuals, 43 were from the Khamisiyah sub-group, 26 from the Non-Khamisiyah sub-group and 29 from the Non-Deployed sub-group (Table 2). These study participants were all veterans or active duty personnel from either the western states (WA, OR and CA) or the southeast (NC or GA). The Level II clinics were held from January 26, 1999 to June 14, 2000 at the Mark Hatfield Research Building at Oregon Health Sciences University (renamed July 1, 2001, Oregon Health & Science University), Portland, Oregon.

All Level II study participants had an electroencephalogram (EEG) recorded while awake with eyes closed at rest, or while performing a simple auditory perception task. The EEG data were segmented and edited for frequency analysis and application of Fast Fourier Transform analysis. Data were entered into a Microsoft Access™ database. Subjects also had upper and lower limb somatosensory evoked potential testing. Relevant peak latency and amplitude data were similarly entered into the database. Lastly, subjects had transcranial magnetic motor evoked potentials performed, with muscle recordings from

abductor pollicis brevis, adductor digiti minimi, tibialis anterior and soleus. Relevant onset latency and average peak amplitudes were recorded and similarly entered into the database.

Table 1. State of residence and deployment group for the 98 individuals who completed Level II testing.

State of Residence	Non-Deployed	Non-Khamisiyah	Khamisiyah
Oregon	3	7	6
Washington	6	3	7
California (Sacramento)	5	6	0
California (San Francisco)	4	6	1
North Carolina	1	2	15
Georgia	10	2	13
Total	29	26	43

The disposition summary for the study participants contacted by the Clinical Nurse Coordinator is shown in Table 2. Potential Level II participants were contacted by telephone. The number of calls required to contact a subject ranged up to twelve. Exclusion criteria for level II included, but were not limited to, diabetes mellitus, post-traumatic stress syndrome, sarcoidosis, night or third-shift workers, brain surgery, and the presence of metal plates in the body. Refusals were usually based on the following: lack of interest, foreign assignments, unable to take time from work due to either lack of vacation time or for financial reasons.

Table 2: Disposition summary of contacts and clinic attendance for Level II stratified by state of residence.

State of residence	Attempts to call	Number contacted	Ineligible	Refusals	Agreed to attend	Number attended
OR	29	27	6	4	17	16
WA	39	37	6	12	19	16
CA	44	37	4	7	26	22
NC	43	32	3	5	24	19
GA	56	43	4	10	29	25
Totals	211[§]	176	23	38	115	98[¥]

[§] Total reflects number of potential subjects called. Some subjects were contacted after one call; many were contacted after 4-6 calls, and some were contacted after 10-12 calls.

[¥] Several subjects cancelled one or more times and then did attend. Those subjects were not counted in the cancelled number.

A total of 211 telephone calls was made and 176 (83.4%) potential Level II participants were contacted. Of these 176 contacts, 23 (13.1%) were found to be ineligible, 38 (21.6%) refused to attend and 115 (65.3%) agreed to attend the Level II clinic. Of those who *agreed* to attend, 98 (85%) *participated* in Level II testing. The 17 subjects who agreed to attend and subsequently did not either failed to show (n = 4) or canceled (n = 13).

Complete Factor Analysis on Self-Reported Neurological Symptoms

A factor analysis of self-reported health symptoms was carried out. The results of this analysis, plus a discussion of our results relative to those published by other investigators, are described in an appended manuscript (Shapiro et al., under review).

KEY RESEARCH ACCOMPLISHMENTS

• We constructed a database of 2918 veterans who were contacted by telephone; this includes 1833 telephone interviews of health status and exposures during the Gulf War.

A total of 1833 telephone interviews was completed, but 54 interviews were removed from the study because the deployment information reported by the veteran fell outside the eligible deployment period for the study. The resulting 1779 interviews were obtained from 516 nondeployed veterans, 653 Khamisiyah veterans, and 610 non-Khamisiyah veterans. Significant differences were found between the deployed and non-deployed subjects and between the Khamisiyah and Non-Khamisiyah subjects. Subjects in the three deployment groups differed according to current region of residence. These differences were due in part to the clustering of large numbers of the Khamisiyah population in the southeastern United States compared to the West Coast. Given these significant regional differences, all statistical analyses were adjusted for region of residence.

The Khamisiyah subjects were almost entirely active, regular military (99.4%) versus activated reserve troops. A substantial percent of the nondeployed (30.2%) and the Non-Khamisiyah groups (23.9%) consisted of activated reserve troops. The nondeployed group had a higher proportion of females compared to deployed subjects (10.7% compared to 4.9%, $p < 0.001$). Deployed subjects were slightly younger than nondeployed ($p = 0.015$), and Khamisiyah veterans were younger than those in the Non-Khamisiyah group ($p = 0.010$). Deployed subjects were more likely to be of minority race ($p < 0.001$). Subjects did not differ according to marital status, employment status or rank during the GW. Compared to nondeployed subjects, deployed subjects were slightly more likely to have a high school education or less ($p = 0.002$). Because of these observed differences, all subsequent analyses comparing the health status of the deployment groups were adjusted for region of residence, gender, and age.

• We performed neurobehavioral assessments on 624 participants. Differences among the deployment groups were clouded by differences among ethnic groups and among

comparable ethnic groups across the cities tested.

• The preliminary analysis was performed using data collected from 96 of the original 98 subjects. Results from a single female, the only one in this part of the study, and from a male with incomplete data, were removed for the purposes of data analysis We performed neurological examinations on a subsample of veterans in the Khamisiyah group (n= 42), veterans distant from Khamisiyah (n= 26) and non-deployed veterans (n= 28). Neurological and neurophysiological examinations designed to detect persistent effects of organophosphates revealed no group differences among these three groups.

REPORTABLE OUTCOMES

Analysis of Research Questions Related to the Finding of the CATI Survey

Three research questions were analyzed. The first explored differences in symptoms during the time period of the Khamisiyah detonations and currently among the three study groups. Whereas no symptom differences were evident when subjects in the DoD's broadly defined Khamisiyah group were compared to troops outside the defined area, differences were found between the small number of individuals who witnessed the Khamisiyah detonations and others in the larger Khamisiyah group. The symptom checklist contained 24 items, with 16 reported in excess in the troops involved with or observing the detonation. Of these 16 symptoms, all but 3 have been described as immediate responses to low doses of organophosphates. The symptoms appear to have been mild since no episodes of acute illness consistent with exposure to anticholinesterase agents occurred during the period of the Khamisiyah detonations. A full description of these findings has been published (McCauley et al., 2000).

The second research question explored differences in medical diagnoses and functional status among the three study groups. We evaluated the prevalence of self-reported medical diagnoses and hospitalizations among this Khamisiyah veteran population and among comparison groups of veterans deployed and non-deployed to the S.W. Asia theater of operations. Troops reported to be within 50 kilometers of the Khamisiyah site did not differ from other deployed troops on reports of any medical conditions or hospitalizations in the nine years following the Gulf War. Hospitalization rates among deployed and non-deployed troops did not differ. Deployed troops were significantly more likely to report diagnoses of high blood pressure (OR = 1.7), slipped disk or pinched nerve (OR = 1.5), post-traumatic stress disorder (OR = 14.9), hospitalization for depression (OR = 5.1), and periodontal disease (OR = 1.8) when compared to non-deployed troops. There was a trend for deployed veterans to report more diagnoses of any cancer (OR = 3.04) and heart disease (OR = 2.5). It is our conclusion that these findings do not provide evidence of any long-term health effect associated with exposure to the detonation of chemical warfare agents, but support findings from other investigations of increased morbidity among deployed troops. Though not statistically significant, the prevalence of cancer among this population of deployed troops merits ongoing attention. A copy of this manuscript is appended (McCauley et al., under review).

The third research question was addressed in a set of analyses designed to determine if factor analysis identified a unique "Gulf War Syndrome" among those veterans deployed to the Khamisiyah area and to determine the relationship between those findings and findings from a standard epidemiological analysis of the same data. In addition, a methodology approach was used to examine the behavior of dichotomous data that are often used in surveys of symptoms subjected to factor analysis. Standard factor analysis resulted in identifying three factors from the 19 symptoms used in the analysis, but these factors were not unique to any deployment group. The symptom factors in the Khamisiyah sample were similar to those reported in previous investigations and included: cognitive-psychological symptoms, dysesthesis, and vestibular dysfunction. These factors overlapped significantly with the symptom factors found in the deployed non-Khamisiyah sample and the non-deployed GW veteran sample. The results of the factor analysis did lend support to the findings of our initial analysis that indicated an increased burden of illness among those who witnessed the controlled detonation of munitions known to have contained sarin/cyclosarin (McCauley et al., 2001). Exploring the behavior of dichotomous variables subjected to factor analysis showed that the standard criteria used to determine factors and the dominant variables within them may be inappropriate in this case. Our conclusion from this work is that while Gulf War veterans appear to suffer an increased burden of illness, there is insufficient evidence to identify a unique Gulf War syndrome. Further, our analysis provides evidence of the limited ability of standard factor analysis to contribute meaningfully in this area. A copy of the manuscript is appended (Shapiro et al., under review).

Analysis of Level II Neurophysiological Data

We performed neurological examinations on a subsample of veterans in the Khamisiyah group (n= 42), veterans distant from Khamisiyah (n= 26) and non-deployed veterans (n= 28). Neurological and neurophysiological examinations designed to detect persistent effects of organophosphates revealed no group differences among these three groups. Furthermore, within the group receiving examinations, the seven veterans who witnessed Khamisiyah had similar neurological functioning to that of others who received clinical examinations. These findings are consistent with those reported in a study of the postwar hospitalization experience of Gulf War veterans exposed to chemical munitions destruction at Khamisiyah [1]. A copy of the manuscript describing these findings is appended (Spencer, 2000).

Analysis of the EEG data focused on relative activity in three separate frequency bins (alpha = 8-13 Hz, beta = 14-30 Hz, and theta = 4-9 Hz). Activity level for each frequency range was measured under three different conditions in three brain regions (occipital-central, mid-temporal, parietal-occipital). Multivariate analysis of variance (MANOVA) was used to assess differences among deployment groups with respect to relative activity. No significant differences among deployment groups were found in any of the brain regions under any experimental condition (p-values ranged from 0.08 to 0.73). Comparisons were also made between the non-deployed sub-group and a deployed sub-group formed from pooling Khamisiyah and non-Khamisiyah veterans. There were

no significant differences found between these two groups (p-values ranged from 0.10 to 0.90). A final comparison made between Khamisiyah veterans who took part in, or observed, the demolition of Bunker 73 (n = 7) and those who did not (n = 25) showed no significant differences with respect to relative activity (p-values ranged from 0.21 to 0.93).

Somatosensory evoked potentials for these 96 subjects were analyzed using the same techniques. Veterans from each deployment group had similar lower and upper limb latencies (p-values = 0.15 and 0.58, respectively), though a definite age effect exists (p-value = 0.006 and 0.007 for lower and upper latencies). Comparisons using other group classifications showed similar results.

CONCLUSIONS

Veterans who participated in or who witnessed the demolition at Khamisiyah in 1991 were more likely to report historical or extant symptoms when compared to veterans from other military units. These results should be viewed cautiously because they are based on symptoms recalled nine years after the event without precise characterization of exposure. Nonetheless, our findings suggest that symptoms consistent with low-level sarin exposure may have initially occurred, and health effects may have persisted, in veterans who were nearest to the demolition activity. No evidence was found of extant damage or dysfunction of neural pathways with reported or known susceptibility to sarin or other organophosphates. No conclusions could be drawn from the results of neurobehavioral examination because of differences among nominally similar groups residing in different regions of the country.

Several studies investigating Gulf War illness have used factor analysis to identify specific groups of complaints or symptoms within the population of GW veterans. A factor analysis performed upon binary data, such as the presence or absence of a given health complaint, must be interpreted with caution as the technique was intended for use with continuous data. Our work used simulations to estimate the number of genuine symptom groups that may be expected when factor analysis is performed on binary data. This technique also allowed us to empirically derive a critical value for discrimination between dominant and secondary symptoms within a given factor.

Taken in concert with our previous studies [3,4], we have been unable to find any association between persistent unexplained illness in Gulf War veterans and exposures to chemicals that inhibit cholinesterase activity, including sarin, organophosphate pesticides, and pyridostigmine bromide [2].

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APPENDICES

Copies of the following papers are appended.

McCauley LA, Lasarev M, Sticker D, Rischitelli DG, Spencer PS (under review) Illness experience of Gulf War veterans possibly exposed to chemical warfare agents. Am. J. Prev. Med. Under review.

McCauley LA, Rischitelli DG, Lambert WE, Lasarev M, Sticker DL, Spencer PS Symptoms of Gulf War Veterans possibly exposed to organophosphate chemical warfare agents at Khamisiyah, Iraq. Int. J. Occup. Environ. Health 7, 79-89, 2001.

Shapiro SE, Lasarev MR, McCauley L. Factor analysis of Gulf War illness: What does it add to our understanding of deployment health? Am. J. Epidemiol. Under review.

Spencer PS (representing a group of clinical and non-clinical research scientists). Single and multiple symptom-based case definitions describe persistent unexplained illness in Gulf War veterans. Proceeding of the Conference of Illnesses among Gulf Wear Veterans: A Decade of Scientific Research, Alexandria, VA, January 24-26. The Research Working Group: Military and Veterans Health Coordinating Board, pp. 34-36, 2001.

[Am. J. Prev. Med. Under review]

ILLNESS EXPERIENCE OF GULF WAR VETERANS POSSIBLY EXPOSED TO CHEMICAL WARFARE AGENTS

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Illness Experience of Gulf War Veterans Possibly Exposed to Chemical Warfare Agents

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Total text word count::	3074
Total pages:	22
Tables:	3

Abstract:

During the 1991 Gulf War, some Allied troops were potentially exposed to chemical warfare agents as the result of the detonation of Iraqi munitions at Khamisiyah. The authors conducted a computer-assisted telephone survey of 2,918 Gulf War veterans from Oregon, Washington, California, North Carolina, and Georgia to evaluate the prevalence of self-reported medical diagnoses and hospitalizations among this potentially exposed population and among comparison groups of veterans deployed and non-deployed to the S.W. Asia theater of operations. Troops reported to be within 50 kilometers of the Khamisiyah site did not differ from other deployed troops on reports of any medical conditions or hospitalizations in the nine years following the Gulf War. Hospitalization rates among deployed and non-deployed troops did not differ. Deployed troops were significantly more likely to report diagnoses of high blood pressure (OR = 1.7), slipped disk or pinched nerve (OR = 1.5), post-traumatic stress disorder (OR = 14.9), hospitalization for depression (OR = 5.1), and periodontal disease (OR = 1.8) when compared to non-deployed troops. There was a trend for deployed veterans to report more diagnoses of any cancer (OR = 3.04) and heart disease (OR = 2.5). These findings do not provide evidence of any long-term health effect associated with exposure to the detonation of chemical warfare agents, but support findings from other investigations of increased morbidity among deployed troops. Though not statistically significant, the prevalence of cancer among this population of deployed troops merits ongoing attention.

Key Words: Gulf War; morbidity, hospitalization, Khamisiyah; chemical warfare agents; organophosphates

Since the conclusion of the Gulf War in 1991 there has been much investigation into the excess illness that has been reported among troops in the United States, Great Britain, Canada, and the Netherlands. Studies have consistently reported an excess of health symptoms among troops deployed to SW Asia,[1-5] yet there is scarce evidence that these symptoms have resulted in more illness, diagnosed diseases, hospitalizations or deaths.[6-10] Still, reports continue to surface concerning about the extent of neurological impairment, the incidence of cancer, and other diseases among this population.[11-17]

The purpose of this investigation was to examine the relationship between low-dose exposure to anticholinesterase agents and subsequent effects on health . The only known exposure to anticholinesterase chemical warfare agents was the destruction of munitions containing 8.5 metric tons of sarin/cyclosarin housed in Bunker 73 at Khamisiyah, Iraq on March 4, 1991 and additional destruction of sarin/cyclosarin rockets in a pit at Khamisiyah on March 10, 1991.[18-19] In 1999 we conducted a telephone survey of GW veterans currently residing in five US states as part of a larger study investigating neurological and neurophysiological signs and symptoms in troops who may have been exposed to low-levels of anticholinesterase agents. We surveyed troops who were reported to be in the vicinity of Khamisiyah in the first half of March 1991, troops who were not reported to be in the area at that time and troops that were not deployed to SW Asia. Veterans who had participated in or witnessed the demolitions in 1991 were found to be more likely to report certain neurological symptoms than were veterans from other military units.[20] This article discusses the telephone survey results describing the overall current self-reported health status of these three populations including medical diagnoses, hospitalizations and functional status.

Design

Study Population

To be eligible for the study veterans had to have been on active or reserve duty in the U.S. Army or National Guard during the combat period of the GW and the weeks immediately after (January 1, 1991-March 31, 1991). All eligible veterans had to be residents of OR, WA, CA, GA, or NC at the time of the telephone interview. The choice of the states that were sampled was determined in part by the geographic distribution of veterans who had served in the Khamisiyah area during March 1991 and the logistics of planning the parent study, that incorporated field testing in sites in each of these states. All eligible veterans also had to have a telephone number that could be identified by common search mechanisms.

The sampling frame for the study was obtained from the Operation Desert Shield/Storm database (ODSS) provided by the Defense Manpower Data Center (DMDC) and maintained by the United States Department of Defense (DoD). The DMDC provided study investigators with three data sets (described below) that listed demographics and military information for personnel potentially eligible for inclusion in our study.

1. **Khamisiyah population**: We obtained a datatape from the DoD for all OR, WA, NC, GA and CA residents who were part of the approximately 20,000 individuals within a 50 km radius of Khamisiyah between March 4 to March 13, 1991 (n = 5328). The large majority of the population had NC and GA addresses (n = 4178).

2. **Non-Khamisiyah population**: These individuals were defined as those military personnel deployed to S.W. Asia during the GW combat period. Veterans who were also in the Khamisiyah database population and those who did not serve in the theater of operations during

the period of January 1, 1991 to March 31, 1991 were removed, resulting in a population of 143,910 veterans residing in OR, WA, CA, NC and GA.

3. Nondeployed population: We obtained the identifiers of 814,331 military personnel who did not serve in the GW theater of operations but who were on active duty or were activated some time during the GW period. This database consisted of 814,331 currently active, reserved or retired service personnel residing in OR, WA, CA, NC and GA.

Sampling Pool

We pulled random samples from each of these three groups, to track current telephone information in order to establish a sampling pool for the telephone survey. The telephone sample pool was assembled with the goal of interviewing approximately 600 individuals in each of the three deployment groups. Five steps were used to locate valid addresses and telephone numbers for entering veterans into our telephone sampling pool as previously described.[20]

Computer-Assisted Telephone Interview (CATI)

Letters introducing the study were mailed to all individuals in our sampling pool; this included a toll-free telephone number and postage-paid return card by which the subject could provide a new address and updated telephone information. Within 5 to 7 days of the mailing, a call was made to the subject to explain the study, obtain consent, and to conduct the telephone computer-assisted interview (CATI) or arrange a time that was convenient for the interview. Clearwater Research, Inc. conducted the telephone interviews using trained and experienced personnel. Real-time telephone monitoring was conducted utilizing the LanAssist™ software to verify accuracy of interviewer data input. The Waksberg module for CATI was implemented to ensure

that calls to individuals were attempted at different times and different days. The interviews were conducted from October 1998 to April 1999.

Study instrument

We adapted an existing survey instrument used in a population-based study of GW veterans in the northwest U.S.[21-23] This instrument was designed to gather detailed information on the nature of GW-related environmental exposures, including exposures to biological and chemical factors, and to prescription and experimental medications taken in theater. The reliability and validity of information reported on the questionnaire have been addressed elsewhere in detail.[22-23] The original questionnaire was adapted to obtain more information on personnel movement in the Khamisiyah area, including exposure to detonation of ammunition bunkers.

A substantial portion of the questionnaire addressed health both in-theater and after return from S.W. Asia, including current health symptoms. The interview also contained questions on conditions that had been diagnosed by a physician since the Gulf War, employment status, hospitalizations, and disability.

We obtained information on the reliability of self-reported medical diagnoses by re-contacting a random sample of 150 veterans who participated in the interview 6 months after initial contact. The subjects in the reliability sample were asked identical questions relating to the presence of medical conditions included in the CATI interview.

Results

Our telephone-interview sampling pool consisted of 923 Khamisiyah veterans, 927 non-Khamisiyah veterans and 1,369 non-deployed (ND) veterans with valid telephone numbers. We were unable to enter a large number of veterans into our sampling pool because of unavailable or non-locatable telephone numbers. We have previously reported that veterans with locatable phone numbers were more likely to have college or advanced degrees, to be married, to be Caucasians, and to be male.[22] We were able to contact 2,918 of the 3,219 veterans (90.6%) by telephone. Of this group, 530 were found to be ineligible due to not being in the Army or National Guard during the GW (n = 274), being a veteran of prior conflicts and not the GW (n = 231), having language or hearing problems that preventing administration of a telephone interview (n = 24), or they were deceased (n = 1). Of the 2,918 individuals reached by telephone, 555 refused to complete the interview (19.0%), resulting in 1833 completed telephone interviews. Veterans agreeing to participate in the interview were more likely to be older, female, and Caucasians than non-participants. The comparison of study participants and non-respondents has been previously reported.[20]

Of the 1833 completed interviews, 54 subjects were removed from the analyses because the deployment information provided by the respondent fell outside the dates of interest in the study. The background characteristics of the remaining 1,779 participants are shown on Table 1. Significant differences were found between all deployed and ND subjects and between the KHAM and N-KHAM subjects. Subjects in the three deployment groups differed according to current region of residence. These differences were due in part to the clustering of large numbers of the Khamisiyah population on the eastern seaboard of the continental United States

compared to the west coast. Given these significant regional differences, all subsequent analyses were adjusted for region of residence. The KHAM subjects were almost entirely active, regular military (99.4%) versus activated reserve troops. The ND group had a higher proportion of females relative to deployed subjects. Deployed subjects were slightly younger than ND subjects and KHAM subjects were slightly younger than N-KHAM subjects. Deployed subjects were more likely to be of minority race ($p < 0.001$). Subjects did not differ according to marital status, employment status or rank during the GW. Deployed subjects were slightly more likely to have a high school education, or less, when compared to ND subjects ($p = 0.022$). Because of these observed differences, all subsequent analyses comparing the health status of the deployment groups were adjusted for region of residence, gender, and race.

Health Effects

Table 2 compares the reported medical conditions diagnosed by a physician since the GW. KHAM subjects did not differ from N-KHAM subjects on reports of any medical condition. Overall, deployed subjects (KHAM and N-KHAM combined) were significantly more likely to report diagnoses of high blood pressure (OR = 1.7, 95% CI 1.3-2.4), slipped disk or pinched nerve (OR = 1.5, 95% CI 1.1-2.0), post-traumatic stress disorder (OR = 14.9, 95% CI 4.7-47.3), hospitalization for depression (OR = 5.1, 95% CI 1.2-21.6), and periodontal disease (OR = 1.8, 95% CI 1.2-2.7) when compared to nondeployed subjects. There was a trend for deployed veterans to report more diagnoses of any cancer (OR = 3.04, 95%CI .89-10.4) and heart disease (OR 2.5, 95% CI 1.0-6.0). When the rates of high blood and periodontal disease were adjusted for current or ever-smoking status the odds of reporting high blood pressure was 1.7 (95% CI 1.3-2-4) and periodontal disease was 1.8 (95% CI 1.2-2.7).

Our test-retest reliability coefficients indicated excellent reliability for diagnoses of cancer (kappa = .96), hepatitis (kappa = .94), diabetes mellitus (kappa = .81), high blood pressure (kappa = .74), heart disease (kappa = .66), lung disease (kappa = .72) PTSD (kappa = .66), major depression (kappa = .74), and alcohol or substance abuse (kappa = .60). Moderate reliability was found for slipped disk/pinched nerve (kappa = .59).

The deployed group reported 21 cases (1.7%) of cancer compared to 3 (0.5%) in the ND group. Because of this apparent, but non-significant trend in differences in all cancers in the deployed versus ND groups, we contacted each veteran who reporting a cancer diagnosis to obtain details on year of diagnosis and type of cancer. We obtained details on the cancers in 20 of the 24 cases. When all skin cancers (n = 7) and cases that were not confirmed at the time of telephone follow-up (4) were removed from the analyses, the odds of having cancer in the deployed versus non-deployed groups was 4.94 (95% CI = .6-38.1). There was no apparent trend for any specific type of cancer. The prevalence of cancer within age strata was compared to the 1994 Connecticut Cancer Prevalence Rates per 1000 for males. Table 3 compares the all-cancer prevalence rates with the 1201 deployed male veterans in our sample. The rates appear to be elevated particularly in the 45-49, 55-59, and 60-64 age groups, but these comparisons are very unstable due to the number of cases observed in each strata.

Other health and functional status indicators were also compared among deployed and non-deployed veterans. In the deployed subjects, 24.2% reported that their general health was fair to poor compared to 14.4 % of the ND (OR = 1.90, 95% CI = 1.44-2.51). In the deployed group,

16.9% reported that they had moderate to extreme impairment of functional ability compared to 11.5% of the ND group. Rates of current and/or past smoking did not differ among the three groups. Groups did not differ in the likelihood of taking prescription medication for chronic health problems. The likelihood of having been hospitalized since the Gulf War did not differ among the groups, with 36.8% of the KHAM and 32.1% of the N-KHAM being hospitalized compared to 31.4% of the ND. Service-connected disability did not differ among the groups (28.5% of KHAM, 22.4% of N-KHAM and 25.5% of ND).

Discussion

Our findings suggest that veterans who were possibly exposed to low levels of chemical warfare agents do not differ from other deployed veterans on any health indicator, including self-reported medical diagnoses, hospitalization or disability. However, significant differences were observed in the comparison of chronic diseases among veterans deployed during the GW and veterans who were not deployed. We found that veterans deployed to the GW were more likely to report medical diagnoses of high blood pressure and there was a trend, though insignificant for more diagnoses of heart disease. A previous study of hospitalization data from the Department of Defense, the Department of Veterans Affairs and California hospitals did not observe any increased proportional morbidity related to diseases of the circulatory system among deployed veterans.[9] Similarly, a study of Kansas veterans found no excess hypertension among deployed veterans.[25] However, a study of United Kingdom troops reported an association between deployment to the GW and high blood pressure, which remained after controlling for socio-demographic and lifestyle variables.[3] Our findings suggest that high blood pressure and perhaps

heart disease may be more common among deployed U.S. troops, but the excess disease is not necessarily reflected in rates of hospitalization.

An increased risk for back disorders (slipped disc or pinched nerve) has also been reported in United Kingdom troops with an odds ratio of 1.5 (1.3-1.7) in deployed troops versus non-deployed troops.[3] An increased risk of post-traumatic stress disorder (PTSD) and depression has been observed by multiple investigators.[1,25] A study of veterans resident in Iowa reported significantly higher prevalence rates of symptoms of depression and PTSD.[1] However, deployed U.S. veterans were not more likely to be hospitalized for these diagnoses in the proportional morbidity hospitalization study conducted by Gray et al.[9] While this study also reported excess disorders of tooth development among deployed veterans, our observation of excess periodontal disease has not been reported previously. Rates of periodontal disease remained elevated after controlling for current of ever smoking, the most commonly recognized risk factor.[26] Stress and inadequate coping mechanisms have been related to the risk of periodontal disease. Others investigators have described the role of genetics, stress, infection, immunodeficiency and the development of periodontal disease.[26-29] The risk of periodontal disease in deployed troops merits additional inquiry since periodontal status is an independent predictor of mortality.[30]

While statistically nonsignificant, the odds ratio of cancer among deployed GW veterans merits attention. On the telephone survey, we found 3 cancers in our non-deployed group for a rate of 0.6/100 and 21 cancers in our deployed group for a rate of 1.7/100. The estimated prevalence of any cancer in veterans from Iowa conducted in 1996 was 1.0 per 100 (s.d. = 0.3) in deployed regular military and 1.9 per 100 (s.d. = 0.3) in deployed reservists. The prevalence of cancer in

non-deployed troops was 1.0/100 (s.d. = 0.3) in regular military and 0.6 (s.d. = 0.2) in non-deployed reservists.[1] Gray et al, 1996 reported a slightly higher risk of hospitalizations for neoplasms during 1991 among GW veterans with compared to non-deployed troops.[6] However this excess hospitalization for neoplasms was not observed in their 2000 follow-up PMR study of hospitalizations of GW veterans in three hospital systems.[9] Our study, along with other cross-sectional studies of GW veterans have been limited in their ability to form conclusions regarding the potential risk of cancer due to the small sample size and limited number of cases of cancer. Prospective studies of sufficient numbers of GW veterans with medical record validation are needed to determine there is a risk of cancer outcomes in this population.

In a study of the post-deployment experience of GW veterans in three hospital system, Gray proposes that the differences in PMRs in the VA medical system may be due to eligibility and socioeconomic reasons, and that the VA medical system population is much less healthy than ~~is~~ the general US population.[9] Gray proposed that the registry screening may have disproportionately inflated hospitalizations among GW veterans with diagnoses of the respiratory system, digestive system, and symptoms, signs and ill-defined conditions. Our results indicate that while hospitalization rates do not differ between deployed and non-deployed groups, significant differences in chronic health conditions may be emerging.

As suggested previously by Gray et al.,[6-7,9] there appears to be an absence of a large increase in illnesses requiring hospitalization among GW veterans. Gray studied hospitalization rates immediately following the GW, and four years later, with no indication that deployed veterans have higher rates of hospitalization for medical conditions. While the frequencies of certain

medical diagnoses are elevated in deployed troops, our study did not find that these elevations result in increased rates of hospitalization or disability.

There are several limitations to our study design that could have affected the results. Our sample was limited to those individuals whose telephone numbers could be tracked using common search mechanisms. We did not track individuals through state motor vehicle records and funding for the investigation was insufficient to individually track veterans without telephones by notifying next-of-kin. Therefore, our sample is not representative of the entire population of troops serving in the GW. Previous investigators have documented the extent of bias associated with non-use of extensive tracking measures with veteran populations.[31] In a follow-up telephone interview of Vietnam veterans, subjects that could not be located without intensive tracking efforts were more likely to share baseline traits predictive of increased mortality when compared to subjects who were located within two weeks. However, no significant differences in health outcomes were observed between easy-to-locate and hard-to-locate respondents.

A strength of our study is that it compares non-deployed troops with deployed troops, a subgroup of which could possibly have been exposed to chemical warfare agents. While the long-term sequelae of low-dose exposure to chemical warfare agents is an area of scientific debate,[32] the results of our study indicate that the exposed Khamisiyah group does not currently appear to be at increased risk for the development of chronic disease. However, our results suggest that troops deployed to S.W. Asia are reporting excess medical diagnoses of high blood pressure, slipped disc or pinched nerve, post-traumatic-stress disorder, hospitalization for depression, and periodontal disease. The prevalence of cancer among this population merits ongoing attention.

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Table 1. Background characteristics of the study participants by deployment group.

	DEPLOYED			P-VALUES	
	Non-Deployed N = 516 No. (%)	Khamisiyah N = 653 No. (%)	Non-Khamisiyah N = 610 No. (%)	Deployed vs. Nondeployed	Kham vs. Non-Kham
Region of residence					
East coast	342 (66.3)	576 (88.2)	149 (24.4)	**0.001**	**<0.001**
West coast	174 (33.7)	77 (11.8)	461 (75.6)		
Military status in GW					
Active duty	360 (69.8)	649 (99.4)	464 (76.1)	**<0.001***	**<0.001***
Reserve or Guard	156 (30.2)	4 (0.6)	146 (23.9)		
Rank in GW					
Officer	101 (19.6)	86 (13.2)	118 (19.3)	0.054*	0.062*
Enlisted	415 (80.4)	567 (86.8)	492 (80.7)		
Gender					
Male	461 (89.3)	628 (96.2)	573 (93.9)	**<0.001***	0.679*
Female	55 (10.7)	25 (3.8)	37 (6.1)		
Mean Age (s.d.)	39.0 (7.5)	37.8 (7.3)	38.1 (8.3)	**0.015***	**0.010***
Race (5†)					
White	335 (65.1)	432 (66.5)	451 (74.1)	**<0.001***	0.058*
Black	136 (26.4)	147 (22.6)	82 (13.5)		
Other	44 (8.5)	71 (10.9)	76 (12.5)		
Education					
H.S. or less	125 (24.2)	212 (32.5)	152 (24.9)	**0.002***	0.087*
Some College	391 (75.8)	441 (67.5)	458 (75.1)		
Employment Status					
Employed	447 (92.4)	609 (93.3)	558 (91.5)	0.805*	0.904*
Unemployed	18 (3.5)	20 (3.1)	19 (3.1)		
Other	21 (4.1)	24 (4.1)	33 (5.4)		
Marital Status (3†)					
Married	401 (77.9)	549 (84.2)	445 (73.1)	0.255*	0.130*
Separated	9 (1.8)	22 (3.4)	14 (2.3)		
Divorced	41 (8.0)	53 (8.1)	52 (8.5)		
Single	64 (12.4)	28 (4.3)	98 (16.1)		

* Adjusted for region of residence.
† Missing data

Table 2. Frequency (%) of diagnosed medical conditions reported by GW veterans

Symptom	Frequency (%)			OR (95% CI)	
	Non-Deployed N = 516	Khamisiyah N = 653	Non-Khamisiyah N = 610	Deployed. vs. Non-Deployed*	Khamisiyah vs. Non-Khamisiyah*
Cancer	0.6	1.2	2.1	3.0 (0.9,10.4)	0.4 (0.1,1.4)
Hepatitis	1.2	1.5	2.6	2.0 (0.8,5.4)	0.6 (0.2,1.5)
Liver disease	1.0	1.1	1.5	1.3 (0.4,3.5)	1.0 (0.3,3.7)
Diabetes	2.5	2.3	2.3	1.0 (0.5,2.0)	1.0 (0.4,2.8)
High blood pressure	12.2	18.7	16.4	1.7 (1.3,2.4)	0.9 (0.6,1.3)
Heart disease	1.2	3.2	1.8	2.5 (1.0,6.0)	0.8 (0.3,1.8)
Lung disease	1.7	2.6	3.3	1.8 (0.9,3.8)	0.3 (0.2,0.8)
Slipped disk/pinched nerve	12.6	16.5	18.7	1.5 (1.1,2.0)	0.7 (0.5,1.0)
Other neurological disease	1.4	2.1	2.5	1.8 (0.8,4.1)	0.6 (0.2,1.6)
Epilepsy or seizures	0.2	0.5	0.5	2.7 (0.3,23.3)	0.5 (0.1,4.1)
Peripheral neuropathy	2.1	2.0	2.8	1.2 (0.6,2.3)	1.0 (0.4,2.6)
Post-traumatic stress disorder	0.8	7.0	8.7	14.9 (4.7,47.3)	1.0 (0.6,1.7)
Major depression with hospitalization	0.6	1.7	2.0	5.1 (1.2,21.6)	1.1 (0.4,3.3)
Obsessive compulsive disorder	1.0	1.8	1.3	1.7 (0.6,4.6)	1.6 (0.5,5.3)
Other psychiatric disease or psychosis	2.3	3.6	5.2	1.7 (0.9,3.3)	0.6 (0.3,1.2)
Multiple chemical sensitivity	1.2	1.1	1.3	1.0 (0.4,2.6)	1.4 (0.3,5.7)
Alcohol or substance abuse	2.1	4.1	3.6	1.7 (0.8,3.3)	2.0 (0.9,4.2)
Head trauma with loss of consciousness > 30 min.	2.1	2.1	1.0	0.8 (0.3,1.6)	1.1 (0.3,3.5)
Periodontal disease	6.6	8.6	12.1	1.8 (1.2,2.8)	0.6 (0.4,1.0)

* Adjusted for age, gender, race, and region of residence.

Table 3. Comparison of 1994 Connecticut Cancer Prevalence Rates per 1000 and Rates per 1000 among Male Deployed Gulf War Veterans

Age (Males) (missing 2)	25-29 n = 213	30-34 n = 314	35-39 n = 237	40-44 n = 188	45-49 n = 162	50-54 n = 57	55-59 n = 19	60-64 n = 9
All Cancers Connecticut Data	4.00	5.60	6.67	9.60	14.5	23.4	38.1	69.1
Male Veterans	_	3.18	-	10.64	24.7	17.5	52.6	222.2
# Reported Cases among Male Veterans	0	1	0	1	4	1	1	2

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Original Articles

Symptoms of Gulf War Veterans Possibly Exposed to Organophosphate Chemical Warfare Agents at Khamisiyah, Iraq

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During the 1991 Gulf War, some Allied troops were potentially exposed to sarin/cyclosarin as the result of the destruction of Iraqi munitions at Khamisiyah. To evaluate the prevalence of past and current symptoms known to be associated with exposure to these chemical warfare agents, the authors conducted a computer-assisted telephone survey of 2,918 U.S. Gulf War veterans. Veterans who had participated in or witnessed the demolition in 1991 were more likely to report historical or extant symptoms than were veterans from other military units. These results should be viewed cautiously because they are based on symptoms recalled nine years after the event without precise characterization of exposure. Nonetheless, the findings suggest that symptoms consistent with low-level sarin exposure may have initially occurred, and health effects may have persisted in the veterans who were nearest to the demolition activity. Further research is warranted. *Key words*: Gulf War; health symptoms; Khamisiyah; chemical warfare agents; organophosphates.

INT J OCCUP ENVIRON HEALTH 2001;7:79–89

In the last decade, there has been increasing attention given to the potential health effects of low-dose exposures to organophosphate (OP) chemicals. These concerns have been heightened as a result of possible low-level exposures to chemical weapons during the Gulf War (GW)[1-6] and following the release of chemical warfare agents (CWAs) on civilians by terrorists in Japan.[7,8] There are also concerns regarding the potential for adverse health effects arising from the ongoing destruction of stockpiled CWAs in the United States, Russia, and elsewhere.[9-11]

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Funding source: U.S. Army Medical Research and Materiel Command, DAMD17-97-7353.

Numerous hypotheses have been advanced to explain the apparent excess of unexplained health symptoms in Gulf War veterans who were deployed to Southwest Asia. Several investigations have explored the possibility that the symptoms reported by these veterans are related to low-dose exposures to CWAs and other chemical agents.[2-6] After years of denying the occurrence of low-dose exposures to CWAs, the U.S. Department of Defense (DoD) revealed to the Presidential Advisory Committee on Gulf War Veterans' Illnesses (PAC)[1] that, on March 4, 1991, U.S. personnel destroyed munitions containing 8.5 metric tons of sarin/cyclosarin housed in Bunker 73 at Khamisiyah, in Coalition-occupied Iraq. On March 10, 1991, additional sarin/cyclosarin rockets were destroyed in a pit at Khamisiyah.[12,13] At the time of the detonations, the DoD was not aware the munitions contained CWAs. In October 1991, a United Nations Special Commission (UNSCOM) team inspected the Khamisiyah site and found evidence of damaged and intact rockets containing sarin/cyclosarin. The PAC concluded evidence of CWA release at Khamisiyah was overwhelming and that exposure should be presumed for nearby troops.[1] Given the uncertainty concerning the atmospheric dispersion of CWA from the demolition on March 10, 1991, the DoD decided to be conservative and notify all the approximately 20,000 individuals who had been operating within a 50-km radius of Khamisiyah between March 4 and March 13, 1991.[14] The notification informed them of their possible exposure to low levels of CWAs and the availability of clinical examinations by the DoD or the U.S. Department of Veterans Affairs.[15]

The possibility of residual neurologic symptoms from low-dose sarin/cyclosarin exposure was first raised in the 1980s in a series of reports from the National Academy of Sciences addressing long-term health effects from short-term exposures to chemicals used in warfare.[16-18] The possibility of CWA exposure as an explanation for the chronic health problems being reported by GW veterans has also been proposed.[19,20] Veterans of the GW had additionally been exposed to OP insecticides (chlorpyrifos), non-OP insect repellants such as *N,N*-diethyl-

m-toluamide, and the carbamate pyridostigmine bromide (PB) as a nerve-agent-antidote enhancer.

In 1999, we conducted a telephone survey of GW veterans currently residing in five U.S. states as part of a larger study investigating neurologic and neurophysiologic signs and symptoms in troops that may have been exposed to low levels of anticholinesterase warfare agents. We surveyed troops that were reported to have been in the vicinity of Khamisiyah in the first half of March 1991, troops that were reported not to have been in the area at that time, and troops that had not been deployed to Southwest Asia. Among the deployed troops, we also identified veterans who reported that they had witnessed or had been involved in the detonations at Khamisiyah. This paper presents the telephone survey results describing symptoms experienced during the time period of the Khamisiyah detonations and current self-reported health of these three populations.

DESIGN

Study Population

To be eligible for inclusion in the study, veterans had to have been on active or reserve duty status in the U.S. Army or National Guard during the combat period of the GW and the weeks immediately thereafter (January 1, 1991–March 31, 1991). All eligible veterans had to be residents of Oregon, Washington, California, Georgia, or North Carolina at the time of the telephone interview. The choice of the states that were sampled was determined in part by the geographic distribution of veterans from units that had served in the Khamisiyah area and the location of planned field testing sites in each of these states as part of the larger study. The sampling frame for the study was obtained from an Operation Desert Shield/Storm database (ODSS) provided by the U.S. Defense Manpower Data Center (DMDC) and maintained by the DoD. The DMDC provided study investigators with three data sets listing identifying demographics and information for personnel potentially eligible for inclusion in our study.

Khamisiyah population (KHAM). This study population was based on the report that certain U.S. troops were likely to have sustained low-level exposures to sarin/cyclosarin following ground-based detonation of chemical munitions at Bunker 73 in the first two weeks of March 1991.[1] This is the only documented exposure of GW veterans to nerve agents in the Southwest Asia theater of operations. In the fall of 1996, the DoD designated the units believed to be within a 50-km radius of the Khamisiyah Ammunition Storage Point between March 1 and March 15, 1991, and used this designation to create a database of individuals who potentially had been exposed to the nerve agents. These individuals were contacted by the DoD in early 1997 and told that they had been within an area where low-dose CWA exposure might have occurred. We obtained a datatape from the DoD of all OR, WA, NC, GA, and CA residents in the Khamisiyah database (n = 5,328) as the first step of identifying our target population. The majority of the population had NC or GA addresses (n = 4,178). Veterans designated by the DoD as being within the 50-km radius of Khamisiyah were considered to be part of a conservative estimate of the individuals who would be most likely to have sustained low-dose exposures to the CWA release arising from munitions destruction.

Non-Khamisiyah population (N-KHAM). These individuals were defined as those military personnel deployed to the Southwest Asia theater during the GW combat period. We removed from this database all veterans who were also in the KHAM population and those who had not served in the theater of operations during the period January 1, 1991, to March 31, 1991; this resulted in a population of 143,910 veterans residing in OR, WA, CA, NC, and GA. It was assumed that N-KHAM veterans would have had no known exposure to nerve agents but might have been exposed to PB and/or OP insecticides.

Nondeployed population (ND). We obtained the identifiers of 814,331 military personnel who had not served in the GW theater of operations but who had been on active duty or who had been activated during the GW period. This database consisted of 814,331 currently active, reserve, or retired servicemen residing in OR, WA, CA, NC, and GA.

Sampling Pool

Pulling random samples from each of these three groups, we tracked current telephone information to establish a sampling pool for the telephone survey. To participate in the computer-assisted telephone survey, all potential subjects were required to have telephone numbers that could be located by common search mechanisms. The telephone sample pool was assembled with the goal of interviewing approximately 600 individuals in each of the deployment groups. Subjects who were interviewed were subsequently invited to participate in another phase of the study that included neurobehavioral testing in their cities of residence.

Locating and Recruitment of Sample

We used five steps to locate and validate addresses and telephone numbers prior to entering veterans into the telephone sampling pool. First, addresses supplied by the DoD were updated by Equifax using each veteran's social security number. Telematch provided telephone numbers matched by name and address. Telephone numbers were also searched on the World Wide Web (WWW) using search engines such as www.anywho.com (AT&T) and www.bigfoot.com. All individuals who did not respond to initial telephone attempts were retraced using U.S. Inter-

nal Revenue Service records. TransUnion provided telephone numbers for updated addresses. All addresses and/or telephone numbers were used in the case of multiple telephone numbers and/or addresses for individuals.

Computer-assisted Telephone Interview (CATI)

Letters introducing the study were mailed to all individuals in our sampling pool with requests to the postal service for forwarding and address correction. The letters also included a toll-free telephone number and postage-paid return card with which the subject could provide new address and telephone information. Within five to seven days of the mailing, a call was made to the subject to explain the study, obtain consent, and conduct the telephone computer-assisted interview or arrange a time that was convenient for the subject.

A private survey firm, Clearwater Research, Inc., based in Boise, Idaho, conducted the telephone interviews using trained and experienced personnel. Clearwater implemented systematic interviewer monitoring to ensure the highest levels of data quality and integrity. Immediate feedback was provided to the interviewers to maintain and improve standardized interviewing techniques. Real-time telephone monitoring was conducted, and LanAssist™ software was used to verify accuracy of interviewer data input.

The Waksberg module[21] for CATI was implemented to ensure that calls to individuals were attempted at different times and on different days. In addition to varying the dates and times, it did not allow more than three call attempts to any individual in a single eight-hour shift and required one attempt on a weekend.

Potential subjects were carefully screened to ascertain study eligibility based on self-reported military status. To be considered eligible, subjects had to report active or reserve status in the U.S. Army between the time period of August 1, 1990, and June 30, 1991. Consent statements were verbally recorded and the interview was conducted at that time or at the subject's earliest convenience. The average interview lasted 25–30 minutes. The interviews were conducted from October 1998 to April 1999.

Study Instrument

We adapted an existing GW survey instrument used in a population-based study of GW veterans in the northwest United States.[22-24] This instrument was designed to gather detailed information about the nature of environmental exposures during the GW. The survey instrument posed questions about service and duty during the GW, living conditions in the GW, combat exposures, and heat and sand exposures. Exposures to biologic and chemical factors, including prescription and experimental medications taken in-theater, were also assessed in detail. The reliability and validity of information reported on the questionnaire have been presented elsewhere.[23,24] The original questionnaire was adapted to obtain more information about troop movements in the Khamisiyah area, including exposure to detonation of ammunition bunkers.

Deployed subjects were queried regarding their general health and symptoms during the first two weeks following the ground war (Desert Storm), the time period in which the Khamisiyah detonations occurred. The 24-item checklist included mild and moderate symptoms known to be associated with CWA exposures and symptoms that have not generally been associated with exposures to anticholinesterase agents.[16] Immediate or short-term effects of sarin vapor exposure include marked miosis, conjunctival congestion, ciliary spasm, headache, watery nasal discharge, and respiratory symptoms as a result of bronchoconstriction and increased bronchial secretion. As systemic absorption of low doses of the agents occurs, anorexia, nausea and vomiting, abdominal cramps, and diarrhea can result.[16] With percutaneous absorption of the agents, localized sweating and muscular fasciculation are generally the earliest manifestations.[16] Based on this information about the effects of low-dose exposure to sarin, we included 13 items on the checklist (vision problems, tearing of the eyes, reddening of the eyes, headache, runny nose, coughing, muscle twitching, muscle cramping/weakness, sweating of hands and feet, tingling of hands or feet, nausea, and abdominal cramping).

In addition to the likelihood of a veteran's experiencing any one of these symptoms on the checklist, an OP-affected case definition was developed that included any report of three or more of the ocular and respiratory effects that generally appear first after aerosol or vapor exposure to low doses of OP chemical warfare agents.[16] These symptoms included vision problems, reddening or tearing of the eyes, headache, watery nasal discharge, and respiratory effects associated with the inhibition of synaptic acetylcholinesterase at peripheral muscarinic sites[25] (Table 1).

The 24-item checklist also had items that have been reported to be associated with low-level exposures to mustard agents: skin burns, eye injury, and irritation of the respiratory tract.[17] Skin vesiculation is a delayed effect. Items included on the checklist were sunburn-like changes, coughing, tearing of the eyes, reddening of the eyes, hoarse voice, and blisters on the skin.

A second checklist obtained information about current health symptoms. We adapted the current-health-symptom checklist that we had previously used in studies of unexplained illness in GW veterans[23] (Bourdette D, McCauley L, Barkhuizen A, et al. Symptom factor analysis, clinical findings, and functional status in a population-based case–control study of Gulf War unexplained illness. Unpublished observations) to include more specific neurologic symptoms as explored by Haley et al.[26]

Statistical Analysis

Categorical data were analyzed using chi-squared tests.

TABLE 1 Case Definition for Signs and Symptoms Associated with Low-level Exposures to Organophosphate Chemicals*[16,25]

Checklist Symptom	Anticholinergic Action
Vision problems	Impaired vision due to marked pupillary constriction, miosis
Tearing of the eyes	Ocular effect due to conjunctival congestion from direct contact of organophosphates with mucous membranes
Reddening of the eyes	Ocular effect due to conjunctival congestion from direct contact of organophosphates with mucous membranes
Headache	Frontal headache associated with ciliary spasm
Runny nose	Rhinorrhea or watery nasal discharge resulting from direct contact of the organophosphates with nasal passages
Coughing	Respiratory effects associated with combination of bronchoconstriction and increased bronchial secretion

*Veterans met the case definition if three or more of these symptoms were reported to occur during the two-week period following the Gulf War ground conflict (Desert Storm).

Odds ratios and confidence intervals were adjusted for potential confounders (age, gender, region of residence) and estimated using logistic regression. The only continuous variable, age, was analyzed using *t*-tests. All analyses were performed using S-PLUS.[27]

RESULTS

The sampling pool for telephone interview consisted of 3,219 veterans (923 KHAM, 927 N-KHAM, and 1,369 ND) with telephone numbers tracked and located using Telematch, Equifax, IRS, Transunion, and/or Internet search engines. We were unable to enter a large number of veterans into our sampling pool because of unavailable or untraceable telephone numbers. We compared veterans with locatable telephone numbers with those who could not be easily located. Veterans with locatable telephone numbers were more likely to have college or advanced degrees (24.0% compared with 15.4%, $p < 0.001$), to be married (57.2% compared with 47.2%, $p < 0.001$), to be Caucasian (68.8% compared with 60.1%, $p < 0.001$), and to be male (93.5% compared with 91.4%, $p = 0.002$).

We contacted by telephone 2,918 of these 3,219 veterans (90.6%). Of these 2,918 individuals, 530 were contacted but found to be ineligible because they had not been enrolled in the Army or National Guard during the GW ($n = 274$), they were veterans of prior conflicts and not the GW ($n = 231$), they had language or hearing problems that prevented administration of a telephone interview ($n = 24$), or they were deceased ($n = 1$). Of the 2,918 individuals reached by telephone, 555 refused to complete the interview (19.0%), resulting in 1,833 completed telephone interviews. Participants in the telephone survey, when compared with non-responders or persons who refused to participate, were more likely to be Caucasian (69.7% compared with 59.8%, $p < 0.001$) and to be on active versus reserve duty (83.1% compared with 73.4%, $p < 0.001$). There was no difference in the background characteristics of the initial 1,524 responders compared with the 309 responders who were located only after more intensive tracking.

Characteristics of the Study Sample

A total of 1,833 interviews was completed, but 54 interviews were removed from the study because the deployment information reported by the veterans fell outside the eligible deployment period for the study. The resulting 1,779 interviews were obtained from 516 ND, 653 KHAM, and 610 N-KHAM veterans. The background characteristics of the participants in the study are shown in Table 2. Significant differences were found between the deployed and non-deployed subjects and between the KHAM and N-KHAM subjects. Subjects in the three deployment groups differed according to current region of residence. These differences were due in part to the clustering of large numbers of the KHAM population in the southeastern United States compared with the West Coast. Given these significant regional differences, all subsequent analyses were adjusted for region of residence. The KHAM subjects were almost entirely active, regular military (99.4%) versus activated reserve troops. A substantial percentage of the ND (30.2%) and the N-KHAM (23.9%) were activated reserve troops. The ND group had a higher proportion of women compared with the deployed group (10.7% compared with 4.9%, $p < 0.001$). The deployed subjects were slightly younger than the ND subjects ($p = 0.015$), and the KHAM veterans were younger than the N-KHAM veterans ($p = 0.010$). The deployed subjects were more likely to be of minority race ($p < 0.001$). The subjects did not differ according to marital status, employment status, or rank during the GW. Compared with ND subjects, the deployed subjects were slightly more likely to have a high school education or less ($p = 0.002$). Because of these observed differences, all subsequent analyses comparing the health status of the deployment groups were adjusted for region of residence, gender, and age.

Exposure to Chemical Warfare Agents

The survey contained several questions about location and work during and after the GW ground conflict. Figure 1 shows that to be within 50 km of Khamisiyah, one would be situated north of the Iraq border (the distance from the Khamisiyah site to the Iraqi border is

TABLE 2 Characteristics of the Study Sample

	Non-deployed (*n* = 516) No. (%)	Deployed		*p* Values	
		Khamisiyah (*n* = 653) No. (%)	Non-Khamisiyah (*n* = 610) No. (%)	Deployed vs Nondeployed	Khamisiyah vs Non-Khamisiyah
Region of residence					
East coast	342 (66.3)	576 (88.2)	149 (24.4)	0.001	<0.001
West coast	174 (33.7)	77 (11.8)	461 (75.6)		
Military status in Gulf War					
Active duty	360 (69.8)	649 (99.4)	464 (76.1)	<0.001*	<0.001*
Reserve or guard	156 (30.2)	4 (0.6)	146 (23.9)		
Rank in Gulf War					
Officer	101 (19.6)	86 (13.2)	118 (19.3)	0.054*	0.062*
Enlisted	415 (80.4)	567 (86.8)	492 (80.7)		
Gender					
Male	461 (89.3)	628 (96.2)	573 (93.9)	<0.001*	0.679*
Female	55 (10.7)	25 (3.8)	37 (6.1)		
Age, mean (SD)	39.0 years (7.5)	37.8 years (7.3)	38.1 years (8.3)	0.015*	0.010*
Race (5†)					
White	335 (65.1)	432 (66.5)	451 (74.1)	<0.001*	0.058*
Black	136 (26.4)	147 (22.6)	82 (13.5)		
Other	44 (8.5)	71 (10.9)	76 (12.5)		
Education					
High school or less	125 (24.2)	212 (32.5)	152 (24.9)	0.002*	0.087*
Some college	391 (75.8)	441 (67.5)	458 (75.1)		
Employment status					
Employed	447 (92.4)	609 (93.3)	558 (91.5)	0.805*	0.904*
Unemployed	18 (3.5)	20 (3.1)	19 (3.1)		
Other	21 (4.1)	24 (4.1)	33 (5.4)		
Marital status (3†)					
Married	401 (77.9)	549 (84.2)	445 (73.1)	0.255*	0.130*
Separated	9 (1.8)	22 (3.4)	14 (2.3)		
Divorced	41 (8.0)	53 (8.1)	52 (8.5)		
Single	64 (12.4)	28 (4.3)	98 (16.1)		

*Adjusted for region of residence.
†Missing data.

approximately 200 km). Differences were observed between the status provided by the DoD and that reported by the veterans. In the KHAM group ($n = 653$), 50 subjects reported that they had never been in Iraq (7.8%) suggesting some degree of misclassification regarding potential CWA exposure status. In the N-KHAM group ($n = 610$), 69 subjects (11.3%) reported that they had been within 50 km of Khamisiyah. Of these 69 individuals, 53 reported that they had been in Iraq, making this assertion plausible. Furthermore, 15 of the 69 reported that they had been involved in or watched the Khamisiyah detonations. Changes in group assignment were not made based on these reporting differences, but are relevant in judging the significance of the observed odds ratios of group assignment and health status.

Subjects deployed to the GW were queried regarding work activities and potential exposure to CWAs. Table 3 shows that the KHAM and N-KHAM groups were similar in regard to reports of hearing chemical alarms, using MOPP gear during alarms, and seeing signs warning of chemical, nuclear, and biologic threats. Among the KHAM subjects, 17.9% reported seeing the explosion of suspected CWA-agent-containing land mines, compared with 8.4% of the N-KHAM subjects ($p < 0.001$). The KHAM subjects also reported more frequently that they had entered destroyed enemy missile launch sites (11.8%) compared with 7.7%, $p = 0.02$). Of the N-KHAM subjects, 115 (18.9%) reported that their work had involved demolition of enemy weapon or munition bunkers, compared with 38% of the KHAM group ($p < 0.001$). Of these 115 individuals, 36 reported that they had been in the Khamisiyah area during the demolition, suggesting again some degree of misclassification of exposure status.

Health Effects

Table 4 compares the self-reported symptoms in the KHAM and N-KHAM groups during that time period. No difference was found in the reported symptoms between these two groups when adjusted for age, gender,

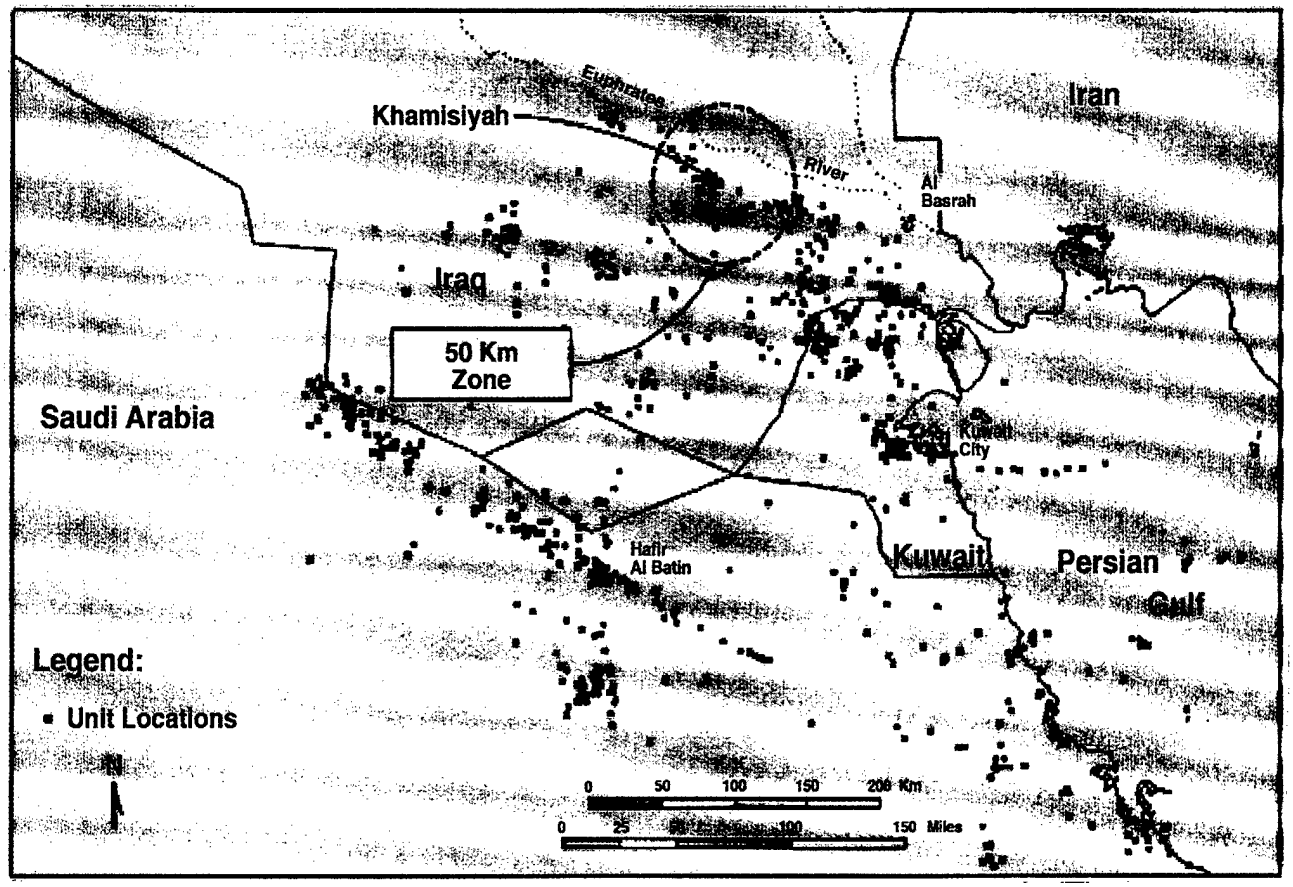

Figure 1—Khamisiyah, Iraq, detonation site and 50-km notification circle.

and region of residence. Of the 653 individuals in the KHAM group, 162 individuals reported that they had been involved in or watched the Khamisiyah operations, 405 reported they had not been involved or had not watched, and the remainder was unsure. Table 4 also compares the symptoms of the 162 individuals in the subgroup who had been involved in or watched the Khamisiyah detonations with those of the 405 non-involved individuals. The KHAM-activity subgroup (KHAM witness) relative to the KHAM non-witness subgroup was more likely to report that during the first two weeks after the ground war they experienced vision problems (OR = 2.4, 95% CI = 1.3–4.2), headaches (OR = 2.6, 95% CI = 18.3–3.8), nausea (OR = 2.3, 95% CI 1.4–3.6), abdominal cramping (OR = 2.4, 95% CI = 1.5–3.8), runny nose (OR = 1.9, 95% CI = 1.2–3.0),

TABLE 3 Ammunition Detonation Work of Veterans and Their Exposures to Chemical Warfare Agents during the Gulf War

	Khamisiyah (n = 653) No. (%)	Non-Khamisiyah (n = 610) No. (%)
Saw the explosion of any suspected chemical land mine*	117 (17.9)	51 (8.4)
Entered a destroyed enemy missile launch site†	77 (11.8)	47 (7.7)
Heard chemical alarms	379 (58.0)	330 (54.1)
Issued MOPP gear for protection from chemical attack	651 (99.7)	608 (99.7)
Ever failed to use MOPP gear during alarm	66 (10.1)	69 (11.4)
Saw nuclear, biologic or chemical weapon warning signs	149 (22.8)	150 (24.6)
Work involved demolition of enemy weapons or munitions bunkers*	248 (38.0)	115 (18.9)
Involved in the munitions-demolition activity at Khamisiyah?* (responded only if yes above)		
Yes	41 (16.5)	6 (5.2)
No, but observed the demolition	121 (48.8)	30 (26.1)
No/not sure	86 (34.7)	79 (68.7)

*$p < 0.001$, †$p = 0.02$ for comparisons between Khamisiyah and non-Khamisiyah.

TABLE 4 Frequencies and Adjusted Odds Ratios of Self-reported Symptoms Experienced during the First Two Weeks after the Ground War in Deployed Khamisiyah and Non-Khamisiyah Veterans

	Khamisiyah (n = 653) vs Non-Khamisiyah (n = 610)			Khamisiyah Witness (n = 162) vs Khamisiyah Non-witness (n = 405)		
	Frequency (%)			Frequency (%)		
	Khamisiyah	Non-Khamisiyah	OR (95% CI)*	Witness	Non-Witness	OR (95% CI)†
Vision problems	8.3	6.6	1.0 (0.6,1.8)	14.2	6.7	2.4 (1.3,4.2)
Headache	33.8	33.4	1.0 (0.7,1.3)	50.0	27.6	2.6 (1.8,3.8)
Nausea	17.3	15.9	1.0 (0.7,1.4)	26.5	13.6	2.3 (1.4,3.6)
Abdominal cramping	16.1	14.9	1.1 (0.7,1.7)	24.7	11.6	2.4 (1.5,3.8)
Increased hunger	13.5	12.5	1.1 (0.7,1.7)	17.9	12.1	1.6 (0.9,2.6)
Increased salivation	4.1	2.5	1.8 (0.8,4.3)	6.8	3.5	2.0 (0.9,4.5)
Runny nose	14.2	15.6	1.0 (0.7,1.6)	21.6	12.6	1.9 (1.2,3.0)
Muscle twitching	13.2	11.0	1.2 (0.8,1.8)	20.4	10.6	2.0 (1.2,3.3)
Muscle cramping/weakness	18.8	15.2	1.2 (0.8,1.7)	27.8	10.6	2.1 (1.4,3.3)
Heart palpitations	10.7	7.7	1.1 (0.7,1.8)	13.6	9.9	1.4 (0.8,2.4)
Increased urination	12.9	11.6	0.8 (0.5,1.3)	19.1	10.4	2.1 (1.3,3.8)
Sweating of hands or feet	16.5	17.2	0.9 (0.6,1.3)	25.3	14.3	2.0 (1.3,3.1)
Tingling of hands or feet	14.6	10.5	1.3 (0.8,2.0)	23.4	11.1	2.5 (1.5,4.0)
Rashes	19.3	17.5	1.0 (0.7,1.5)	29.0	16.8	2.0 (1.3,3.2)
Bad dreams	15.8	20.8	0.7 (0.5,1.0)	21.6	14.3	1.5 (1.0,2.5)
Vertigo	5.4	3.8	1.5 (0.7,3.0)	9.3	3.5	2.7 (1.3,5.8)
Slurred speech	3.4	3.4	0.9 (0.4,2.0)	4.9	2.5	1.8 (0.7,4.9)
Nosebleed	3.5	5.4	0.5 (0.2,1.0)	3.7	2.5	1.4 (0.5,4.1)
Sunburn-like changes	3.2	4.4	0.6 (0.3,1.3)	6.2	2.7	2.3 (1.0,5.7)
Coughing	26.3	22.3	1.2 (0.9,1.7)	38.3	23.4	2.1 (1.4,3.1)
Tearing of the eyes	15.3	14.1	1.1 (0.7,1.6)	19.8	14.1	1.4 (0.9,3.2)
Reddening of the eyes	18.5	15.4	1.1 (0.8,1.7)	23.5	16.0	1.8 (1.2,2.8)
Hoarse voice	10.1	13.1	0.6 (0.4,1.0)	17.3	8.4	2.5 (1.4,4.3)
Blisters on the skin	3.8	2.8	1.1 (0.5,2.4)	8.0	2.7	3.3 (1.4,7.7)

*Adjusted for age, gender, and region of residence.

†Adjusted for age and gender, Khamisiyah subjects who witnessed demolition activity near Khamisiyah, compared with Khamisiyah subjects who did not witness demolition activity.

muscle twitching (OR = 2.0, 95% CI = 1.2–3.3), muscle cramping/weakness (OR = 2.1, 95% CI = 1.4–3.3), increased urination (OR = 2.1, 95% CI = 1.3–3.8), sweating of hands or feet (OR = 2.0, 95% CI = 1.3–3.1), tingling of hands or feet (OR = 2.5, 95% CI = 1.5–4.0), rashes (OR = 2.0, 95% CI = 1.3–3.2), vertigo (OR = 2.7, 95% CI = 1.3–5.8), coughing (OR = 2.1, 95% CI = 1.4–3.1), reddening of the eyes (OR = 1.8 95% CI = 1.2–2.8), hoarse voice (OR = 2.5, 95% CI = 1.4–4.3), and blisters on the skin (OR = 3.3, 95% CI = 1.4–7.7). All but three of these symptoms (rashes, hoarseness, and skin blisters) have been described as effects of exposures to organophosphate CWAs,[25] and all symptoms described as low-dose-exposure first effects were elevated in the KHAM subgroup.

The Khamisiyah-activity subgroup and other Khamisiyah veterans were assessed for the proportions of those reporting three or more of the immediate symptoms associated with airborne organophosphate CWA exposure (vision problems, headache, runny nose, coughing, tearing of eyes, and reddening of eyes). The frequency in the Khamisiyah activity subgroup was 27.8%, compared with a frequency of 15.3% in the other Khamisiyah veterans (OR = 2.13, 95% CI 1.4–3.3).

Table 5 compares the current self-reported health symptoms of the non-deployed subjects with those of the deployed (KHAM and N-KHAM) subjects. Deployed veterans reported significantly higher rates of all health symptoms except recurrent fainting. Among the deployed subjects, KHAM subjects were comparable to N-KHAM subjects with respect to all symptoms, except that the KHAM subjects reported significantly fewer effects from being in confined places.

When the 162 veterans who had been involved in or watched the Khamisiyah detonations were compared with the KHAM veterans who had neither been involved in nor watched the detonations, significant increases were found for reports of tingling or burning sensations of the skin (OR = 1.7, 95% CI = 1.1–2.8), changes in memory (OR = 1.7, 95% CI = 1.2–2.4), difficulty sleeping (OR = 2.0, 95% CI = 1.2–3.5), persistent fatigue (OR = 1.8, 95% CI = 1.2–2.6), depression (OR = 1.6, 95% CI = 1.1–2.4), and bloody diarrhea (OR = 3.1, 95% CI = 1.6–6.0).

DISCUSSION

The search for associations between exposures during the Gulf War and unexplained illness has been an area of

TABLE 5 Adjusted Odds Ratios (95% CI) for Current Health Symptoms According to Deployment and Khamisiyah Status in Gulf War Veterans

	Deployed (n = 1,263) vs Non-deployed (n = 516)*	Khamisiyah (n = 653) vs Non-Khamisiyah (n = 610)*	Khamisiyah Witness (n = 162) vs Non-Khamisiyah Witness (n = 405)†
Tingling, burning, sensation of pins and needles	2.2 (1.6, 3.2)	0.8 (0.6, 1.2)	1.7 (1.1, 2.8)
Numbness or lack of feeling	2.4 (1.7, 3.4)	0.7 (0.5, 1.1)	1.4 (0.9, 2.2)
Loss of muscle strength in arms or legs	3.4 (2.4, 4.9)	1.0 (0.7, 1.4)	1.4 (0.9, 2.2)
Loss of balance or coordination	2.8 (1.8, 4.3)	0.8 (0.6, 1.3)	1.4 (0.8, 2.4)
Dizzy spells	2.4 (1.7, 3.4)	0.8 (0.5, 1.1)	1.5 (0.9, 2.4)
Changes in memory	5.6 (4.3, 7.4)	1.3 (1.0, 1.7)	1.7 (1.2, 2.4)
Difficulty sleeping	4.1 (3.1, 5.5)	1.0 (0.8, 1.4)	2.0 (1.2, 3.5)
Jaundice	3.5 (1.4, 11.8)	0.9 (0.4, 2.2)	Not estimable
Persistent fatigue, tiredness, or weakness	6.2 (4.7, 8.4)	1.0 (0.7, 1.3)	1.8 (1.2, 2.6)
Depression	3.7 (2.7, 5.1)	0.9 (0.6, 1.2)	1.6 (1.1, 2.4)
Fainting	2.5 (0.9, 8.4)	2.0 (0.7, 6.2)	1.1 (0.3, 3.7)
Unusual irritability/anger	4.1 (3.1, 5.6)	1.0 (0.8, 1.4)	1.3 (0.9, 1.9)
Mood swings	4.8 (3.6, 6.7)	1.1 (0.8, 1.5)	1.4 (1.0, 2.1)
Choking sensation	2.1 (1.3, 3.7)	0.9 (0.5, 1.7)	1.6 (0.9, 3.1)
Problems following directions or instructions	4.3 (2.6, 7.6)	1.0 (0.6, 1.5)	1.4 (0.8, 2.4)
Difficulty concentrating	4.3 (3.1, 6.2)	1.0 (0.8, 1.4)	1.3 (0.9, 1.9)
Cramping, aches, pains or stiffness of muscles	2.8 (2.2, 3.8)	1.0 (0.7, 1.4)	1.4 (1.0, 2.1)
Problems breathing, wheezing, coughing, SOB‡	3.5 (2.6, 4.8)	1.1 (0.8, 1.5)	1.5 (1.0, 2.2)
Increased sensitivity to everyday chemicals	3.1 (2.2, 4.3)	1.2 (0.8, 1.6)	1.5 (1.0, 2.3)
Bloody diarrhea	2.3 (1.4, 4.0)	1.1 (0.6, 2.0)	3.1 (1.6, 6.0)
Effects from confined places	3.6 (2.3, 6.0)	0.6 (0.4, 0.9)	1.6 (0.9, 2.7)
Continuous eye irritation or sensitivity	3.5 (2.4, 5.1)	1.1 (0.7, 1.5)	1.2 (0.8, 1.8)
Unexplained periodontal disease	4.1 (2.4, 7.7)	0.9 (0.5, 1.4)	1.7 (0.9, 3.2)
Unexplained weight loss > 10 lb	3.5 (2.2, 6.0)	0.7 (0.4, 1.0)	1.9 (1.0, 3.3)
Unexplained weight gain > 10 lb	2.9 (2.2, 3.9)	1.0 (0.8, 1.4)	1.5 (1.0, 2.2)

*Adjusted for age, gender, and region of residence.

†Adjusted for age and gender, Khamisiyah subjects who witnessed demolition activity near Khamisiyah, compared with subjects who did not witness demolition activity.

‡Shortness of breath.

much research investigation and speculation. The findings from this study provide evidence of possible health effects associated with close proximity to a CWA release point during the Gulf War. Although no symptom difference was evident when subjects in the DoD's broadly defined Khamisiyah group were compared with troops outside the defined area, differences were found between those who had witnessed the Khamisiyah detonations and others in the larger Khamisiyah group. The symptom checklist contained 24 items, with 16 reported in excess in the troops involved with or observing the detonation. Of these 16 symptoms, all but three have been described as immediate responses to low doses of organophosphates.[25] The symptoms appear to have been mild, since no episode of acute illness consistent with exposure to anticholinesterase agents occurred during the period of the Khamisiyah detonations.[1]

Three of the symptoms (hoarseness, rashes, and skin blisters) reported in excess in the two-week period in which the Khamisiyah detonations occurred are difficult to explain as an effect of sarin/cyclosarin exposure. However, hoarseness, skin blisters, coughing, and rashes do form a grouping that is consistent with the signs and symptoms of low-level exposure to mustards.[28] The DoD has denied the presence of a mustard chemical agent at Khamisiyah, although UNSCOM found over 6,000 artillery shells filled with mustard agent in an open area 3 k west of the Khamisiyah bunkers in October 1991. These shells were undamaged and were stored in several stacks/clusters under tarpaulins.[14]

Within the deployed troops that we surveyed, individuals who had been within 50 km of the Khamisiyah detonations did not differ from those in the N-KHAM group in terms of their current health symptoms. However, the troops who had been involved in or watched the Khamisiyah detonations did report excess frequencies of five neurologic symptoms. The chronic effects of low-level exposures to nerve agents have yet to be resolved, but if effects are observable, they would likely be manifest as persistent neurophysiologic or neuropsychologic symptoms.[25] Five of the six symptoms reported in excess among the troops who had been involved in or watched the Khamisiyah detonations fall into this category. The excess in reports of diarrhea has been previously reported in other GW studies,[29-31] but this symptom is not generally thought to be associated with any known long-term effect of organophosphate exposure.

The lack of any detectable increase in symptoms

among the larger Khamisiyah group, when compared with the other deployed troops, could be explained by one of four phenomena:

1. The CWAs released at Khamisiyah were not of significant magnitude to adversely affect troops within 50 km of the detonation site.
2. The 50-km Khamisiyah designation by the DoD was too broad and the database includes too many individuals who were not exposed to the detonated CWAs.
3. The CWAs were not restricted to the Khamisiyah area but were dispersed more widely (thus, could have contributed to the excess of symptoms being reported by deployed veterans of the GW).
4. The symptoms being reported in excess by troops deployed to the GW were caused by other exposures experienced by a wide array of troops in varied geographic areas.

Given the apparent excess in symptoms among those closest to Khamisiyah, it is most likely that the 50-km designation by the DoD was too broad, and that many in that sample were not exposed to detonated CWAs. Dispersion plume modeling of the Khamisiyah detonations has been used to estimate the temporal–spatial movement of releases from the Khamisiyah detonation.[32] In July 1997, the DoD and the U.S. Central Intelligence Agency completed the first modeling for the March 10, 1991, demolition at the Khamisiyah pit. Based on this model, 10,075 of the original 20,000 troops were identified as having been outside the area of the plume. Later modeling incorporated a much larger geographic area than the 50-km focus of our study and extended some distance south of the Iraqi border (more than 200 km from Khamisiyah.[32] Regardless of the results of this and subsequent modeling, our focus on those within 50 km, and specifically those who had been involved with or observed the detonation, probably includes the personnel that were at greatest risk for airborne exposure to CWAs at Khamisiyah.

Another plausible explanation for the lack of difference in health symptoms in the KHAM sample versus N-KHAM subjects is that the symptoms being reported by GW veterans are the result of varying combinations of multiple factors dispersed throughout the theater of operations and not a result of a single or unique exposure, such as the CWA release at Khamisiyah. The nonspecificity of excess symptoms in all deployed troops compared with non-deployed troops most likely reflects multiple nonspecific exposures to a war zone in general. In previous studies, we have demonstrated that unexplained illness in veterans of the GW who have undergone clinical evaluation is most highly associated with clusters of exposures, including sun exposure, combat exposure, and seeking medical attention during the GW (Spencer P, McCauley L, Lapidus J, Lasarev M, Joos S, Storzbach D. Self reported exposures and their association with unexplained illness in a population-based case-control study of Gulf War veterans. Unpublished observations).

Some investigators have postulated that chemical releases during the GW were of a magnitude sufficient to result in long-term health effects on thousands of veterans. Haley and Kurt[2] concluded that the neurologic findings in their sample of 23 veterans with symptoms and 20 controls were compatible with injury to the nervous system from wartime exposure to low-dose combinations of anticholinesterase chemicals. However, other than the Khamisiyah site, there is no evidence that significant CWA exposures occurred during the GW.[1] Our findings suggest that if there were acute symptoms associated with CWA exposure, they occurred predominately in those veterans who had been close enough to be involved with or observe the detonations at Khamisiyah, and the symptoms are not elevated in veterans who had been farther from the site. We are currently undertaking clinical studies to assess whether the presence of neurologic symptoms of organophosphate exposure correlates with electrophysiologic and neuropsychologic evidence consistent with the reported sequelae of symptomatic exposure to sarin.

The results of this study should be considered in light of several limitations in study design that could have influenced the results. Symptom surveys are easily confounded by information, recall, and selection bias. All of the subjects in our KHAM sample had received a notification letter from the DoD informing them that they had been potentially exposed to low levels of CWA. Training materials commonly distributed to all members of the U.S. Armed Forces contain reference to the symptoms associated with CWA exposure. However, to our knowledge, the veterans who had observed and participated in the Khamisiyah detonations had not received any additional information regarding the types of symptoms that might be expected if exposed to low levels of CWA. The potential does exist for military troops that are trained to destroy stores of ammunition to receive more information about the immediate health effects associated with exposure to CWAs. It is also possible that persons who had been involved in or watched the Khamisiyah detonations would have more inherent interest in the study and differ from other subjects in their ability to recall the symptoms that they had experienced. If recall or information bias played a significant role in this investigation, the lack of any obvious overreporting by the larger KHAM group that had received the DoD notification letter compared with the N-KHAM group is striking and difficult to interpret.

Selection bias could be present, since our sample was limited to those individuals whose telephone numbers could be tracked using common search mechanisms. We did not track individuals through state motor vehicle records, and funding for the investigation was not sufficient to track veterans without telephones by notifying next of kin. Therefore, our sample may not be represen-

tative of the entire population of troops serving in the GW. Previous investigators have documented the extent of bias associated with non-use of extensive tracking measures with veteran populations.[33] In a follow-up telephone interview of Vietnam veterans, subjects who could not be located without intensive tracking efforts were more likely to share baseline traits predictive of increased mortality when compared with subjects who were located within two weeks. However, no significant difference in health outcomes was observed between easy-to-locate and hard-to-locate respondents.

Unfortunately, the population of veterans that was in proximity to the Khamisiyah site is currently not evenly distributed throughout the United States. The distribution of the KHAM sample in the southeastern United States could have introduced biases that we cannot recognize or measure. We adjusted all comparisons of symptoms between the KHAM and other groups because of this regional location difference. The differences that we observed within the KHAM group cannot be attributed to region of the country, but could have been confounded by other unrecognized factors. The veterans who had observed and participated in the Khamisiyah detonations were more likely to hold GW job codes for infantry/armor (44.7%) and construction/engineering (15.1%) when compared with the veterans in the larger Khamisiyah group (22.3% infantry/armor and 1.7% construction/engineering). The potential exists for the differences observed in health symptoms during the Khamisiyah detonations and those reported currently to be associated with differences in work exposures between the two groups and not the Khamisiyah detonations specifically.

In summary, we compared the current health symptoms of veterans who had been within 50 km of Khamisiyah with those of veterans not deployed to that area during the two weeks following Desert Storm. No significant difference emerged in current health symptoms or those experienced in the two-week period in which the Khamisiyah detonations occurred. However, there were significant differences in symptom reporting by the subset of veterans who had been involved in or watched the Khamisiyah detonations. While the findings of this study are limited by the passage of more than nine years since the potential exposure to CWAs released from the Khamisiyah detonations, and by the use of self-reported health symptoms, many of the symptoms reported in excess are consistent with those associated with immediate effects of sarin exposure. All but one of the current symptoms reported in excess are consistent with those postulated to be associated with chronic effects of low-dose exposure to organophosphates. These findings have contemporary relevance for potential future military exposures and for populations exposed to organophosphate agents through terrorist activities[7,8] or accidental releases associated with the storage, transport, and handling of chemical warfare agents designated for destruction under treaty agreements.[9,10]

This project was sponsored by research grant DAMD 17-97-1-7353 from the Department of the Army. The contents of this paper do not necessarily reflect the position or the policy of the U.S. Government, and no official endorsement should be inferred.

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[Am. J. Epidemiol. Under review.]

FACTOR ANALYSIS AND GULF WAR ILLNESS: WHAT DOES IT ADD TO OUR UNDERSTANDING OF DEPLOYMENT ILLNESS?

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ABBREVIATIONS:

CWA : chemical warfare agent
DoD : U.S. Department of Defense
DNK : deployed, non-Khamisiyah
FA : factor analysis
GWS : Gulf War syndrome
KHAM : deployed, Khamisiyah
ND : non-deployed
NWIT : non-witnesses of the demolition at Khamisiyah
ODSS : operation Desert Shield/Desert Storm
WIT : witnesses of the demolition at Khamisiyah

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ABSTRACT

This paper presents findings of a factor analysis done on survey data from 1,779 Gulf War veterans. The three purposes of the study were to: (1) determine if factor analysis identified a unique "Gulf War Syndrome" among veterans potentially exposed to chemical warfare agents; (2) determine the relationship between those findings and those from an epidemiological analysis of the same data; and (3) describe the behavior of factor analysis when performed on dichotomous data . The factor analysis identified three factors but they were not unique to any deployment group. A unique pattern of illness was not found for the larger group of veterans potentially exposed to chemical warfare agents, however veterans who witnessed the demolition of CWA's had a greater prevalence of dysesthesia.. An analysis of the performance of dichotomous variables in factor analysis showed the standard criteria used to determine the number of relevant factors and the dominant variables within them may be inappropriate. These results lend support to the finding that while Gulf War veterans appear to suffer an increased burden of illness, there is insufficient evidence to identify a unique syndrome. Further, the results provide evidence of the limited ability factor analysis techniques has to contribute meaningfully in this area.

KEYWORDS

Gulf War Syndrome, factor analysis, unexplained illness, Khamisiyah, chemical warfare agents

WORD COUNT:

Abstract: 204
Manuscript: 3,770

The debate over the presence of a discrete "Gulf War Syndrome" (GWS) persists more than 10 years after the end of Operation Desert Shield/Desert Storm (ODSS). Investigators using both epidemiological methods (1–3) and those using factor analysis (1–6) have found some evidence of increased burden of illness and identified complexes of syndromes among veterans deployed during ODSS. Although the debate about the significance of those findings is ongoing (1, 6–12), investigators continue to find evidence which raises questions about the effects of possible chemical warfare agent (CWA) exposure and the presence of self-reported symptoms among veterans of ODSS (3, 13–16).

Bieliauskas and Turner (7) recommend that research on the current health of Gulf War veterans focus on those most likely to have been exposed to CWAs. One group that fits that criterion is veterans who were deployed to the Khamisiyah area of coalition-occupied Iraq and particularly those who witnessed a controlled detonation of Iraqi munitions later determined to have contained known CWAs.

The U.S. Department of Defense (DoD) released information that on March 4, 1991, U.S. personnel destroyed munitions containing 8.5 metric tons of sarin/cyclosarin housed in Bunker 73 at Khamisiyah, and that on March 10, 1991, additional sarin/cyclosarin rockets were destroyed in a pit also at Khamisiyah (17, 18). At the time of the detonations the DoD was not aware the munitions contained CWAs, but subsequently, a United Nations Special Commission team inspecting the Khamisiyah site found evidence of damaged and intact rockets containing sarin/cyclosarin. The DoD notified all of the approximately 20,000 individuals who were operating within a 50 km radius of Khamisiyah between March 4 and March 13, 1991 of their possible exposure to low levels of CWAs and the availability of clinical examinations by the DoD or the U.S. Department of Veterans Affairs (19, 20).

In a recent study, McCauley et al. (16) reported on the health status of veterans who were within the 50 km radius of Khamisiyah. They noted there was no increased risk of current self-reported symptoms among veterans in the Khamisiyah area over those deployed to the Gulf, but

not to Khamisiyah. Within the Khamisiyah group however, veterans close enough to witness the demolition reported significantly more of 16 different symptoms within two weeks of the demolition than non-witnesses, and all but three of these symptoms were consistent with exposures to organophosphate agents. Eight years after the demolition, these same witnesses reported a significant excess of eight health-related symptoms, some of which could plausibly be related to long term effects of low-dose exposure to CWAs.

This paper presents the results of further analysis of the McCauley, et al. data (16). Our first purpose in this analysis was to subject the self-reported health data of Khamisiyah troops to a factor analysis (FA) to determine if a unique factor, or set of factors, could be said to constitute a "Gulf War Syndrome" in this population. Our second purpose was to explore the relationship between the results of the factor analysis and those reported in the earlier paper by McCauley, et al., especially as they relate to the apparent increase in the presence of certain current symptoms among the veterans who witnessed the detonation. Our last purpose was to examine how factor analysis behaves when the data are dichotomous. The new understandings gained in this last analysis are discussed as they might affect the interpretation of these results and those of earlier studies using factor analysis on similar data.

MATERIALS AND METHODS

Study population

The population consisted of veterans who were on active or reserve duty in the U.S. Army or National Guard during the combat period of the GW and the weeks immediately thereafter (January 1, 1991–March 31, 1991). The sampling frame for the study was obtained from an ODSS database provided by the U.S. Defense Manpower Data Center and maintained by

the DoD. Details of the sampling procedure, location and recruitment of participants, and the use of the computer-assisted telephone interview (including consent procedures) are contained in the earlier report (16).

The final sample used in this analysis is identical to that used in the earlier study by McCauley, et al. and consisted of 1,779 Gulf War era veterans who completed a computer-assisted telephone interview. Of those, 516 veterans were on active duty during the study period, but were not deployed to ODSS (ND), 610 veterans were deployed to SW Asia but not within the 50 km radius around Khamisiyah (DNK), and 653 veterans were deployed within the 50 km radius around Khamisiyah (KHAM). Within the KHAM group, 162 veterans reported they witnessed the Khamisiyah detonations (WIT) and 405 veterans reported that they did not (NWIT).

Study instrument

McCauley, et al. (16) adapted an existing survey instrument used in a population-based study of GW veterans in the northwest U.S.(22–24). The original questionnaire was adapted to obtain more information on troop movements in the Khamisiyah area, including exposure to detonation of ammunition bunkers. In addition, the adaptation of the current health symptom questionnaire included more specific neurological symptoms as explored by Haley et al. in 1997 (7). The reliability of the instrument is reported elsewhere (21–23). Study participants completed two checklists: one of health symptoms they experienced within two weeks of the Khamisiyah detonations, and one of current health symptoms present within the past month. We use only the current health symptoms in our current analysis.

Statistical approach

Factor analysis For the first part of the study, an exploratory factor analysis (FA) of each deployment group (KHAM, DNK, and ND) was performed using SPSS version 10.0 (24). Factors were extracted by principal components and subjected to a varimax rotation (25). Those factors having eigenvalues greater than one and individually accounting for at least five percent of the overall variance were retained. Symptoms with rotated loadings > 0.60 in absolute value were considered "dominant" and served as the defining symptoms for each specific factor. Ordinary least squares (i.e. unweighted regression) (25) was used to calculate factor scores. These decision rules regarding factor retention and identification of dominant and defining symptoms were empirically derived through a *Monte Carlo* simulation, and are more fully described in subsequent paragraphs.

Khamisiyah witness vs. non-witness Although a FA was performed on the entire KHAM group (n = 653), the limited number of veterans who witnessed the munitions detonation (WIT, n = 162) prevented an independent factor analysis of this sub-population. Instead, we determined whether the distribution of factor scores differed significantly between veterans who witnessed the demolition and their non-witnessing counterparts (NWIT, n = 405) using a Wald- Wolfowitz runs test (26). Eighty-six of the 653 veterans in this group were dropped from this part of the analysis because we were unable to reliably ascertain their status as an observer/non-observer of the detonation. We then classified veterans as possessing a particular factor on the basis of their endorsing all of the dominant symptoms within the factor. Using this rule, a veteran could possess several factors simultaneously, a single factor, or none at all. The number of veterans within each combination of factors was then stratified by their status as a witness or non-witness of the demolition activities. The resulting table was analyzed using log-linear models (27) to determine whether the dominant symptoms associated with each factor were independent of a veteran's witness status.

Behavior of dichotomous variables A *Monte Carlo* simulation (28) was used to investigate how factor analytic methods perform using dichotomous data. Artificial data sets were constructed with the same number of records and variables as our original data. Within each artificial set, rows corresponded to individual veterans while columns corresponded to individual symptoms. The number of rows varied according to the deployment group under consideration, while the number of columns (representing symptoms) remained fixed for all deployment groups. Each column of artificial data was randomly generated in such a way as to duplicate the observed proportion of veterans endorsing the corresponding symptom (table 1). Factor analysis was then performed on the artificial data (principal component extraction followed by varimax rotation) and the resulting eigenvalues and rotated loadings were stored. This procedure was repeated 500 times for each of the three deployment groups. The eigenvalues and rotated loadings from these 500 replications provide a "null" distribution of these measures when independently generated dichotomous variables are subjected to a principal component FA accompanied by a varimax rotation. Simulations were performed using the statistical language `R` and the associated `mva` (multivariate analysis) package (29).

RESULTS

Factor analysis

A correlation matrix with 25 symptom variables reported by the entire sample of 1,779 veterans was constructed; six health symptoms had a correlation less than 0.30 with all other symptoms and were removed from further analysis (30). The 19 remaining health symptoms were included in all reported analyses and are listed in table 1.

Factor analysis using principal components extraction with varimax rotation was done initially on the KHAM veteran sample. Three factors were identified with eigenvalues greater than 1.0, and together they accounted for 46.7 percent of the total variance. Using a cutoff of 0.60 for factor loadings, the first factor contained symptoms of unusual irritability/anger, mood swings, changes in memory, persistent fatigue, tiredness or weakness, difficulty concentrating, and depression. This was labeled a "cognitive/psychological" factor.

Factors two and three each contained two variables. The second factor, "dysesthesia," consisted of a tingling, burning, sensation of pins and needles and numbness or lack of feeling. The third factor, labeled "vestibular dysfunction," contained loss of balance or coordination, and dizzy spells.

Factor analysis for both the non-deployed veterans (ND) and deployed non-Khamisiyah veterans (DNK) was performed using the same procedure. Three factors were also identified among the ND veterans, and accounted for 52.2 percent of the overall variance. Symptoms found in the first factor for the ND group were persistent fatigue, tiredness or weakness, depression, unusual irritability/anger, mood swings, difficulty following directions, and difficulty concentrating. As with the KHAM group, this was named a "cognitive/psychological" factor. The second factor, identified as "neuromuscular," contained three symptoms: a tingling, burning, sensation of pins and needles, numbness or lack of feeling, and loss of muscle strength in arms or legs. Factor three had two symptoms as well, and consisted of dizzy spells and increased sensitivity to everyday chemicals. This factor was named "vestibular and other."

Factor analysis of the deployed, non-Khamisiyah (DNK) veterans yielded three factors accounting for 49.8 percent of the total variance. The first factor, again identified as "cognitive/psychological," consisted of changes in memory, difficulty sleeping, depression, unusual irritability/anger, mood swings, and difficulty concentrating. The second factor, also called "dysesthesia," contained numbness or lack of feeling, and a sensation of pins and needles. The third factor, "mixed," contained loss of balance or coordination, dizzy spells, shortness of

breath, and chemical sensitivities. A summary of the factors identified within each group and their symptoms is presented in table 2.

Khamisiyah witness vs. non-witness

Results from the non-parametric Wald-Wolfowitz test indicated no significant differences in the distributions of factor scores between the WIT and NWIT groups (factor one, $p = 0.88$; factor two, $p = 0.19$; factor three, $p = 0.28$). Using log-linear models, we next assessed whether a veteran's status as a witness or non-witness was independent of the endorsement of all dominant symptoms associated with each of the three factors.

The analysis revealed factors one and three ("cognitive/psychological" and "vestibular dysfunction") were unrelated to a veteran's status as a witness ($p = 0.72$), and that factor two ("dysesthesia") was significantly associated with whether a veteran witnessed the demolition ($p = 0.013$). Treating this factor as a response category, we found veterans witnessing the demolition were 2.07 times more likely to endorse both symptoms associated with dysesthesia than were non-witnessing veterans (95 percent confidence interval: 1.16, 3.68).

Performance of factor analysis upon dichotomous variables

The *Monte Carlo* simulations produced similar results for all three populations (KHAM, DNK, and ND), so we report only those from the KHAM group in detail. Again, the purpose of this portion of the study was to investigate how traditional criteria for selecting factors (eigenvalues in excess of one) and subsequently determining which components dominate a given factor (loadings in excess of 0.40) are affected when factor analysis is performed on dichotomous data.

Figure 1 shows the range of eigenvalues from 500 replications of a principal component factor analysis performed on 19 randomly generated dichotomous variables having the same relative frequencies as shown in table 1. Eigenvalues for the first eight factors were always in excess of one; the ninth factor satisfied this criterion 84 percent of the time, and factors 12–19 never produced eigenvalues greater than one. Additionally, the proportion of variance explained by each of the individual factors ranged between 3.4 and 7.6 percent, with an average of 5.3 percent (figure 2). This may be regarded as the "typical" amount of variance explained, per factor, when variables are independent. In general, for randomly generated dichotomous data, the average variance per factor will equal $1/m$, where m defines the number of variables subjected to factor analysis. In this study, 19 variables were examined, so 1/19, or 5.26 percent of the overall variance is expected to be explained. These data indicate that for 19 randomly generated dichotomous variables, five factors are sufficient to account for an average of 32 percent of the total variance.

Table 3 illustrates how the rotated loadings for the first three factors in each of the 500 replications behave. As can be seen, the 90th percentile is not far from 0.60 and approximately 95 percent of the rotated loadings exceed 0.45.

DISCUSSION

Results from factor analysis

The initial factor analysis was performed primarily to determine if one or more discrete factors, or syndromes, emerged that might be used to describe a unique Gulf War Syndrome, especially as found among those veterans with known possible exposure to CWAs. As table 2 demonstrated, while neither the factors nor their component symptoms were identical from

deployment group to deployment group, there was substantial overlap in the symptoms within each factor. These findings are consistent with those of other investigators who performed factor analysis using groups of deployed and non-deployed veterans (1, 2, 4, 6); that is, factors could be identified, but were not unique to a particular deployment group.

Although our findings are largely consistent with those of most other investigators in this field, direct comparisons are impossible for several reasons. First, different investigators have used different symptom lists in their studies. Second, the sizes, sources, and compositions of the samples used in other reports have varied considerably. Third, different investigators used different factor extraction and rotation techniques and different thresholds for factor loadings to identify their syndromes. While these analytic variations are entirely acceptable (30), this, combined with the other differences mentioned above, has resulted in investigators identifying differing numbers of factors containing differing numbers and kinds of symptoms within them. Table 4 summarizes these differences.

The one consistent theme among these studies is that no investigator other than Haley (5) has claimed to have identified a unique Gulf War Syndrome based on the results of a factor analysis. Our findings concur with those of most other investigators. While we too were able to identify clusters of symptoms that appeared to form plausible syndromes, they were not unique to any deployment group, even among those who had the greatest acknowledged likelihood of having been exposed to CWAs.

Comparison of factor analysis with epidemiological analysis

In their earlier paper, McCauley, et al. (16) found some evidence of increased symptoms among KHAM veterans who witnessed the detonation of munitions containing known CWAs compared to other veterans who were within 50 km of Khamisiyah but had not witnessed the detonations. These symptoms are shown in table 5.

The findings in that earlier analysis did not isolate a particular cluster of persistent symptoms that differentiated the KHAM group from either the DNK or ND group, and neither did the factor analysis reported here. However, when we applied the results of the factor analysis to the current symptoms reported by the WIT and NWIT sub-groups, we did find that the WIT group had a significantly greater prevalence of the second factor, dysesthesia. One of the two symptoms in this factor—a tingling, burning, sensation of pins and needles—was identified as significant in the earlier work of McCauley, et al. As the WIT group had a suspected exposure to known CWAs, this finding suggests a need to examine these veterans more closely in order to document the presence of physiological findings consistent with such reported symptoms.

Performance of factor analysis upon dichotomous variables

Factor analysis has been used extensively to test measurement scales and to refine and test constructs such as intelligence and self concept (30, 31). These analyses have been used traditionally with ordinal and interval level data, and at least one statistical program specifies interval level data as the minimum requirement for factor analysis (24). Yet, as was noted in table 4, much of the data used in previously reported factor analyses of GW veterans data operate below this level. Knoke, et al. (6) addressed this issue briefly in their paper; otherwise, previous investigators had little to say about the ways in which factor analysis may perform on non-interval level variables and how that might affect their results.

Our work has shown that application of standard rules to 19 randomly generated dichotomous variables could result in models with five factors which explained approximately 30 percent of the total variance. Even more troubling is the realization that rotated loadings in excess of 0.40, the traditional cut-off, occurred more than 95 percent of the time in our randomly generated data set. Again, as table 4 indicates, previous investigators have used these rules to identify their syndromes and the dominant symptoms within them. If, as our simulation

demonstrated, similar results can be obtained using randomly generated data, we are forced to reconsider the existence of syndromes found in earlier studies, especially those discovered through a factor analysis of dichotomous variables.

These results indicate that one must be very cautious in using factor analysis with these kinds of data; it appears very easy to identify "syndromes" using factor analysis on dichotomous variables when, in fact, the driving mechanism may be random chance. Unfortunately, since Haley's initial paper (5), investigators in this field seem compelled to provide results of factor analysis as a necessary component of analyses related to unexplained Gulf War illnesses. In the absence of more robust decision rules for these kinds of data, the resulting factors may be a rich mixture of randomness which could lead investigators down uninformative paths.

One of the advantages of factor analysis is that it allows investigators to explore their data rather liberally (30). However, Tabachnik and Fidell identified three important limitations to using this technique. First, there is no rigorous criteria against which to test the solution, and as we have demonstrated, without such, certain inferences can be misleading. Second, there are few limitations on the numbers and types of rotations that could be applied, with the final choice of rotation left to the investigator's assessment of its interpretability and scientific utility. Finally, as they identified, factor analysis is often used as a last resort to save "poorly conceived research." While we don't mean to imply the hard work previous investigators has been poorly conceived, we feel there has been a rush to use this technique to try to identify a unique Gulf War Syndrome when more classic epidemiological methods have failed to do so. In fact, given the limitations cited above, it seems that factor analysis has also failed in this task.

Our study is subject to several limitations, most of which are fully detailed in the paper by McCauley, et al. (16). These include all the issues related to self-reported symptoms such as recall and selection bias, and to those sampling biases inherent in using telephone surveys. McCauley and her colleagues also reported possible problems with the geographical distribution

of the KHAM veterans and pointed to possible differences in work exposures between groups that were unrelated to their deployment or witness status.

In addition to these limitations, the results of our simulation are unique to this data set and cannot be taken to establish guidelines for other studies in which factor analysis is performed on dichotomous variables. We urge other investigators performing factor analysis with dichotomous variables to determine how their analysis would behave using simulated data sets of an appropriate size, with individual variables randomly generated to mimic the observed symptom frequencies.

Comments

Research on whether a unique Gulf War syndrome exists tends to be of three types: studies that rely solely on standard epidemiological analyses such as those done by McCauley, et al. (16, 21) and Steele (32); studies that rely solely on factor analysis, such as those done by Haley, et al., Ismail, et al., and Knoke, et al. (4–6); and those that use a combination of these techniques, such as the work done by Fukuda, et al., Doebbling, et al. and Bourdette, et al. (1–3). Taken together, this body of research indicates Gulf War veterans report an increased burden of illness for as much as eight years after their participation in ODSS. However, despite these extensive studies, no one other than Haley has claimed the presence of a unique Gulf War Syndrome, that is, a set of symptoms that appears in these veterans which is different from any other identified disease entity, which only appeared after participation in ODSS, and which does not appear with similar frequency in other populations of veterans or non-veterans.

This is not to diminish the problems encountered by veterans of ODSS. We now know that many of those veterans were possibly exposed to known CWAs, and it is reasonable to expect that some will experience physical symptoms even after more than 10 years' time. Some of these symptoms may be shared with veterans of other conflicts going as far back as the Civil

War (33), and some may be directly related to exposure to organophosphate agents and other CWAs during the ODSS(16) Veterans suffering from symptoms deserve to be thoroughly evaluated and treated for their symptoms regardless of the fact that a unique Gulf War syndrome has yet to be described.

We agree with Steele (32) that problems reported by Gulf War veterans are complex, and that investigators in this field need to consider many possible causes and combinations of causes as the basis for these symptoms. These complexities make it unlikely for any single analytic tool to be the sole source of answers to this continuing controversy.

ACKNOWLEDGMENTS

Funding for this research was provided by the U.S. Army Medical Research and Material Command, DAMD 17-97-7353.

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FIGURE CAPTIONS

FIGURE 1. Eigenvalues from a principal component factor analysis of 19 randomly generated dichotomous variables with the same observed relative frequency as shown for the KHAM group (table 1). Error bars show the range of results from 500 replications.

FIGURE 2. Proportion of variance explained per factor when principal component extraction is performed upon 19 randomly generated dichotomous variables having the same relative frequency as shown for the KHAM group (table 1). Error bars show the range of results from 500 replications.

TABLE 1. Percentage of veterans in each study population endorsing the health symptoms used in the factor analysis.

Symptom	KHAM $n = 653$	DNK $n = 610$	ND $n = 516$
Tingling, burning sensation of pins & needles	16	15	8
Numbness or lack of feeling	17	17	9
Loss of muscle strength in arms/legs	21	21	8
Loss of balance/coordination	12	13	5
Dizzy spells	17	20	9
Changes in memory	51	43	14
Difficulty sleeping	38	38	13
Persistent fatigue, tiredness, or weakness	45	42	11
Depression	26	33	10
Unusual irritability/anger	35	34	11
Mood swings	36	35	10
Problems following directions/instructions	11	14	3
Difficulty concentrating	27	27	8
Cramping, aches, pains or muscle stiffness	33	30	15
Problems breathing	32	27	11
Increased sensitivity to everyday chemicals	23	20	9
Effects from confined spaces	11	18	7
Continuous eye irritation/sensitivity	22	18	7
Unexplained weight gain > 10 lbs (4.5 kg)	28	24	12

TABLE 2. Factors extracted from each of the three study populations.

	KHAM			DNK			ND		
Symptom	Factor 1 *Cognitive-Psychological*	Factor 2 *Dysthesia*	Factor 3 *Vestibular dysfunction*	Factor 1 *Cognitive-Psychological*	Factor 2 *Dysthesia*	Factor 3 *Vestibular and other*	Factor 1 *Cognitive-Psychological*	Factor 2 *Neuro-muscular*	Factor 3 *Mixed*
Unusual irritability/anger	X			X			X		
Depression	X			X			X		
Difficulty concentrating	X			X			X		
Difficulty following directions							X		
Difficulty sleeping				X					
Fatigue	X						X		
Memory changes	X			X					
Mood swings	X			X			X		
Loss of strength								X	
Numbness		X			X			X	
Tingling		X			X			X	
Chemical sensitivity						X			X
Dizziness			X			X			X
Loss of balance			X			X			
Shortness of breath						X			

TABLE 3. Percentiles of rotated factor loadings derived from randomly generated dichotomous data.

	Percentile						
	5	10	25	50	75	90	95
Factor 1	0.46	0.47	0.50	0.53	0.57	0.61	0.62
Factor 2	0.45	0.47	0.50	0.53	0.57	0.60	0.62
Factor 3	0.46	0.47	0.50	0.54	0.58	0.62	0.63

TABLE 4. Summary of studies which used FA on symptoms of Gulf War veterans.

	Haley (5)	Fukuda (1)	Ismail (4)	Bourdette (3)	Doebbeling (2)	Knoke (6)	Shapiro
Sample	Active & retired* (Navy)	Active & reserve (Air Force)	Active†	Active & reserve*	Active & reserve	Active (Navy)	Active
Sample size‡	249	3,255	3,214	407	3,695	1,459	1,779
type of data	Interval §	Ordinal	Ordinal	Dichotomous	Ordinal & dichotomous	Ordinal & dichotomous	Dichotomous
Method	Principal Axis	Principal Component	Principal Factor	Principal Component	unknown	Principal Factor	Principal Component
Rotation	Varimax	Promax & Procrustes	Varimax	Varimax	Varimax & Promax	Varimax	Varimax
Factor loading cut-off	> 0.40	> 0.40	> 0.40	> 0.40	> 0.35	> 0.40	> 0.60
Factors isolated	6	2	3	3	3	5	3
% Variance explained	71	~ 31	~ 20	~ 34	35	80–89	47–52
Factors identified	Impaired cognition; confustion-ataxia; arthro-myo-neuropathy; phobia-ataxia; fever-adenopathy; weakness-incontinence	Fatigue; mood-cognition; musculoskeletal pain	Mood-cognition; respiratory system; peripheral nervous system	Cognitive/psychological; mixed somatic; musculoskeletal	Somatic distress; psychological distress; panic	Insecurity; somatization; depression; obsessive-compulsive; malaise	see table 2

* Sample contains deployed veterans only
† UK veterans
‡ Total sample size of all groups studied.
§ Model based; computed as weighted sum of ordinal item × first stage factor weights.

TABLE 5. Self-reported current symptoms found to be significantly higher among GW veterans witnessing Khamisiyah detonations compared to veterans who did not witness the the detonations.

Symptom	p-value
Tingling, burning sensation of pins & needles	0.024
Changes in memory	0.007
Difficulty sleeping	0.003
Persistent fatigue, tiredness, or weekness	0.002
Depression	0.017
Bloody diarrhea*	0.001

* removed from FA because correlation with all other symptoms was < 0.30.

Figure 1: Eigenvalues from a principal component factor analysis of 19 randomly generated dichotomous variables having the same observed relative frequency as shown for the KHAM group (table 1). Error bars show the range of results from 500 replications.

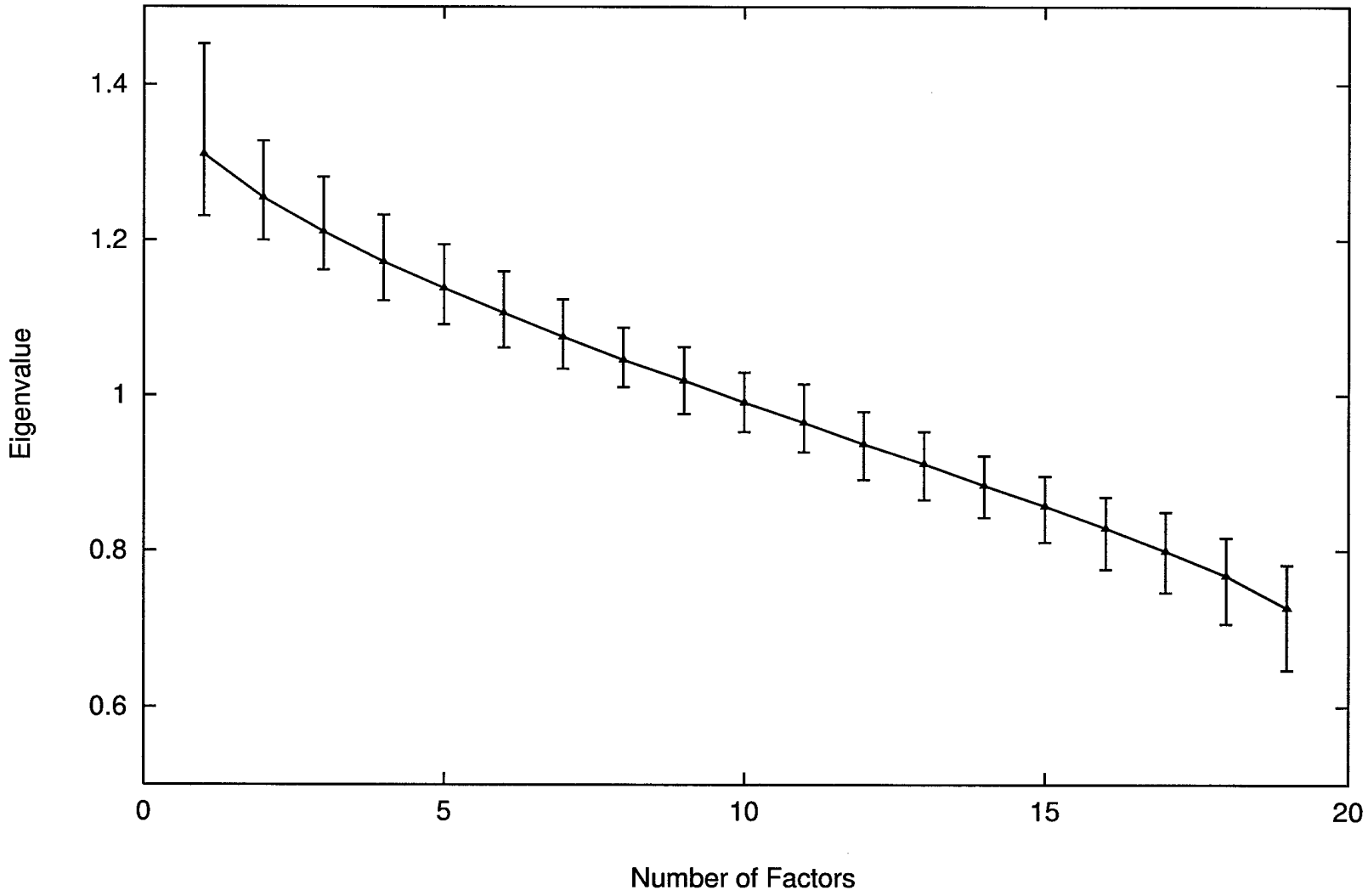
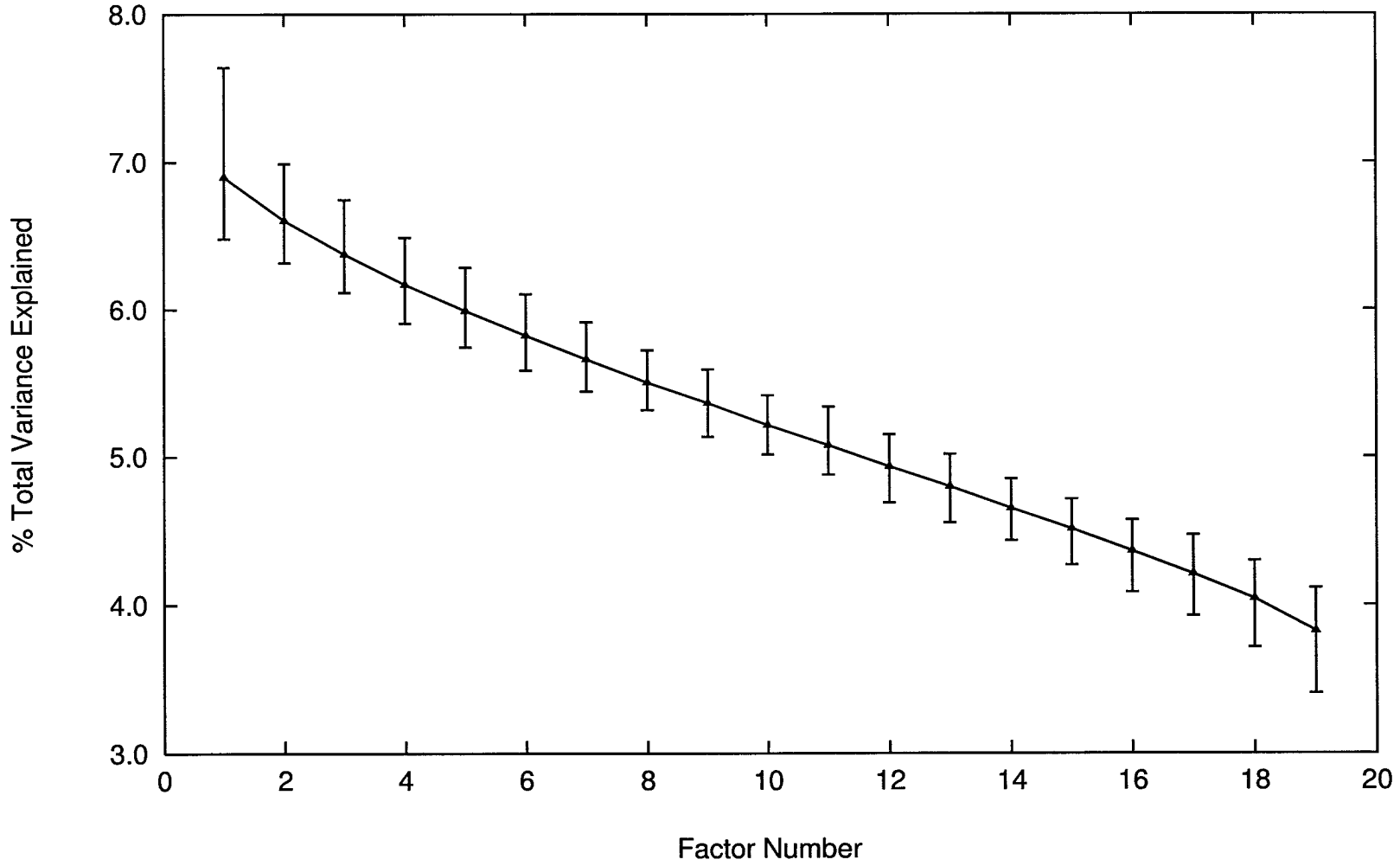


Figure 2: Proportion of variance explained per factor when principal component extraction is performed on 19 randomly generated dichotomous variables having the same relative frequency as shown for the KHAM group (table 1). Error bars show the range of results from 500 replications.



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Conference on Illnesses among Gulf War Veterans: A Decade of Scientific Research

Hilton Alexandria
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January 24-26, 2001

Proceedings

SINGLE AND MULTIPLE SYMPTOM-BASED CASE DEFINITIONS DESCRIBE PERSISTENT UNEXPLAINED ILLNESS IN GULF WAR VETERANS

A multidisciplinary group of clinical and non-clinical research scientists
represented by *Peter S. Spencer

Portland Veterans Affairs Medical Center and Oregon Health Sciences University's (OHSU)
*Center for Research on Occupational and Environmental Toxicology (CROET)
and School of Medicine, Departments of *Neurology and Medicine

Introduction

We have been engaged in studies to determine whether there is a detectable relationship between persistent unexplained illness among Gulf War veterans and their self-reported exposures to multiple stressors (chemical, biological, physical, psychological) in the 1990-91 theater of operations in S.W. Asia. These stressors were present in varying combinations over the course of operations between 8/1/90 and 7/31/91, a period of time characterized here as the Gulf War period.

Case-Control Clinical Study

Our first study analyzed risk factors and persistent unexplained illness in a population-based random sample of Gulf War veterans who underwent clinical evaluation. Multiple risk factors were compared in veterans who met criteria for persistent unexplained illness and in healthy control veterans. Persistent unexplained illness was diagnosed by the Portland study group when musculoskeletal pain, cognitive-psychological changes, *or* unexplained fatigue began during or after deployment to S.W. Asia, persisted for one month or longer, and occurred during the three-month period preceding recruitment into our case-control study. The U.S. Centers for Disease Control and Prevention (CDC) subsequently published a case definition that requires one or more chronic symptoms from *at least two* of three categories (fatigue, cognition, musculoskeletal [1]. We found similar associations between risk factors and persistent unexplained illness as defined by either the Portland or the CDC case criteria.

Our study population was all military personnel deployed to S.W. Asia during the Gulf War period who listed Oregon or Washington as their home-state-of-record at the time of deployment and who were believed to be residing (in 1995) in either of these two states. A random sample of 2343 veterans was selected, with over-sampling of women, reservists and veterans serving in discrete time periods specified below. These veterans were mailed a self-completion questionnaire that solicited information on (a) military service, duties, rank, dates and locations in S.W. Asia, (b) health history and symptoms experienced during and after the Gulf War (c) post-War lifestyle factors and psychosocial adjustment, and (d) exposures in the theater of operations. Only health-related information was used to recruit eligible subjects (N = 799) for the case-control clinical study. A committee that was blind to the exposure histories assigned cases (N=241) and healthy controls (N=113) on the basis of a review of the results of physical, mental status and neurological examinations, clinical laboratory testing, and specialist referrals. Of the 241 cases that met the Portland case definition, 115 met the CDC multi-symptom case criteria. The latter had significantly lower scores on the Armed Forces Qualifying Test and, compared to controls, U.S. Navy veterans were half as likely to be a case as those who served in the Army. There were no significant differences attributable to the primary job classification using either case definition.

Exposure Analysis

Preliminary analyses showed that the proportion of cases was distributed similarly among those deployed in S.W. Asia only within the pre-combat time period (8/1-12/31/90), only within the period surrounding Desert Storm (1/1-3/31/91), only within the period immediately following hostilities (4/1-7/31/91), or for various combinations of the three discrete deployment periods. This suggested that risk factors for persistent unexplained illness were present in S.W. Asia during Desert Shield, Desert Storm, *and* the post-War clean-up period. An examination of environmental factors potentially encountered by U.S. troops in the wartime theater showed that each period contained a different constellation of environmental stressors to which veterans were potentially exposed [3]. Noteworthy is our identification of cases of persistent unexplained illness in veterans who served only in the discrete deployments periods either before or after Desert Storm when there were reportedly no exposures to pyridostigmine bromide (PB), sarin, or botulinum toxoid vaccine [3].

Further analyses examined the relationship between self-reported exposures and persistent unexplained illness in the entire case-control study population For self-reported *single* exposures, the highest odds ratios (> 3.0) for both case definitions were found for the following:

- used insect spray on uniforms (permethrin),
- took more than 21 PB pills,
- contacted diesel/petroleum for six or more days,
- experienced irritated eyes from oil-well fire smoke for six or more days,
- worked in vehicle repair,
- exposed to depleted uranium,
- exposed to artillery smoke,
- exposed to welding fumes,
- sought medical attention during the Gulf War period.

Odds ratios were in general larger using the CDC case definition, but the confidence intervals were wider because of the smaller sample size. Additional odds ratios exceeding 3.0 were generated when the CDC case definition was employed:

- - was outside for 4 or more hours per day,
- - had a problem with flies in the living/eating area,
- - used diethyl-m-toluamide (DEET, insect repellant),
- - had inadequate MOPP gear during a chemical or SCUD alarm,
- - was bitten by snakes or scorpions.

Stress was measured using several measures from the survey questionnaire and scores on the Keane combat-exposure scale, a measure of exposure to potentially life-threatening combat experiences. Those with high Keane scores who used PB were four times more likely to be a Portland- and CDC-defined case than those who did not use PB. No such association was found for those with low Keane scores using either case definition. We were unable to demonstrate any interaction between stress and the *combination* of self-reported use of PB and insecticide. Exposure to PB was *not* significant in a multivariable model.

Forty-two exposure variables were subjected to an agglomerative hierarchical cluster analysis with complete linkage, which resulted in 9 clusters with at least two variables per cluster. Variables retained in the final model were found through backward elimination using the Akaike Information Criterion. Regardless of the case definition, the same demographic characteristics and three exposure clusters appeared in the final model. One cluster focused on seeking medical attention in the Gulf for flu-like symptoms, musculoskeletal problems or for a range of other conditions. With both case definitions, the odds of being a case increased in hand with the number of reasons for seeking medical attention. The second cluster included exposures associated with working outside, including time outside, heat-related symptoms, presence of flies in living/eating areas, and frequency of insect bites. The last cluster reflected combat activities in that it included self-reported exposure to depleted uranium, artillery smoke and fumes, working in areas where chemical warfare agents were found or stored, and the Keane combat-exposure scales. Clusters that did not enter the final model contained variables such as PB use, exposure to smoke from oil-well fires, use of DEET and permethrin, repair of generators and batteries, work with organic solvents and other chemicals, painting, welding, and consumption of alcoholic beverages.

Chemical Weapons

Our second study was designed to detect immediate and persistent health effects of low-dose exposure to chemical warfare agents, notably sarin. We conducted a telephone survey of 2918 Gulf War veterans currently (1998) residing in five U.S. states with over-sampling of veterans who had previously been notified by the U.S. Department of Defense as having been in an area of Coalition-occupied Iraq (Khamisiyah) where low-dose exposure to chemical warfare agents is likely to have occurred. Veterans in the Khamisiyah area during the time period in which artillery shells containing nerve agents were detonated (n= 653) were no more likely to report symptoms when compared to subjects not designated as being in the Khamisiyah area. However, 162 veterans in the Khamisiyah sample who reported they were involved in the detonation activity, or who were close enough to watch the detonations, were more likely to recall experiencing health effects consistent with those resulting from exposure to chemical warfare agents when compared to veterans in the Khamisiyah sample who did not observe the detonations. We performed

neurological examinations on a subsample of veterans in the Khamisiyah group (n= 42), veterans distant from Khamisiyah (n= 26) and non-deployed veterans (n= 28). Neurological and neurophysiological examinations designed to detect persistent effects of organophosphates revealed no group differences among these three groups. Furthermore, within the group receiving examinations, the seven veterans who witnessed Khamisiyah had similar neurological functioning to that of others who received clinical examinations. These findings are consistent with those reported in a study of the postwar hospitalization experience of Gulf War veterans exposed to the detonation at Khamisiyah [2].

Conclusion

Our findings add support to those of others that a case definition based exclusively on the presence of one or more related *symptoms* that arose during or after deployment to S.W. Asia during the Gulf War period accurately describes this illness. Our investigations have not revealed any evidence of an association between persistent unexplained illness in Gulf War veterans and exposures to chemicals that inhibit cholinesterase activity, including sarin, organophosphate pesticides, and PB. Neither these nor other single or combined chemical exposures in the theater of operations adequately explain persistent unexplained illness among Gulf War veterans

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This research was supported by the Department of Veterans Affairs through the former Portland Environmental Hazards Research Center, a joint initiative of the Portland VAMC and CROET at OHSU, and by a research grant to PSS from the U.S. Army Medical Research and Materiel Command (DAMD17-91-1-7353).